21 March 2024
EMA/CHMP/147735/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xtandi

International non-proprietary name: Enzalutamide

Procedure No. EMEA/H/C/002639/II/0063

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
BCR	biochemical recurrence
BICR	Blinded Independent Central Review
BMI	body mass index
CI	confidence interval
COVID-19	illness caused by SARS-CoV-2
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer; also referred to as hormone-sensitive prostate cancer (HSPC)
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HR	hazard ratio
ISS	Integrated Summary of Safety
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer; also referred to as metastatic hormone-sensitive prostate cancer (mHSPC)
MFS	metastasis-free survival
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
nmCRPC	non-metastatic castration-resistant prostate cancer
nmCSPC	non-metastatic castration-sensitive prostate cancer; also referred to as non-metastatic hormone-sensitive prostate cancer (nmHSPC)
nmPC	non-metastatic prostate cancer
NR	not reached
NSAA	nonsteroidal antiandrogen
OS	overall survival
PFS	progression-free survival
PFS2	progression-free survival on first subsequent therapy
PRES	posterior reversible encephalopathy syndrome
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSUR	Periodic Safety Update Report
RMP	risk management plan
rPFS	radiographic progression-free survival

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
TEAE	treatment-emergent adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Astellas Pharma Europe B.V. submitted to the European Medicines Agency on 28 August 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy, for Xtandi, based on final results from study MDV3100-13 (EMBARK); this is a phase 3, randomized, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI and to update the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific advice from the CHMP on 17 January 2013 (EMEA/H/SA/1612/1/FU/2/2012/III). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	28 August 2023
Start of procedure:	16 September 2023
CHMP Rapporteur Assessment Report	14 November 2023
PRAC Rapporteur Assessment Report	17 November 2023
CHMP Co-Rapporteur Assessment	20 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	04 December 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2023
Request for supplementary information (RSI)	14 December 2023
CHMP Rapporteur Assessment Report	22 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Opinion	21 March 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The initial claimed indication was: Xtandi is indicated for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy.

The agreed indication is: Xtandi is indicated as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic

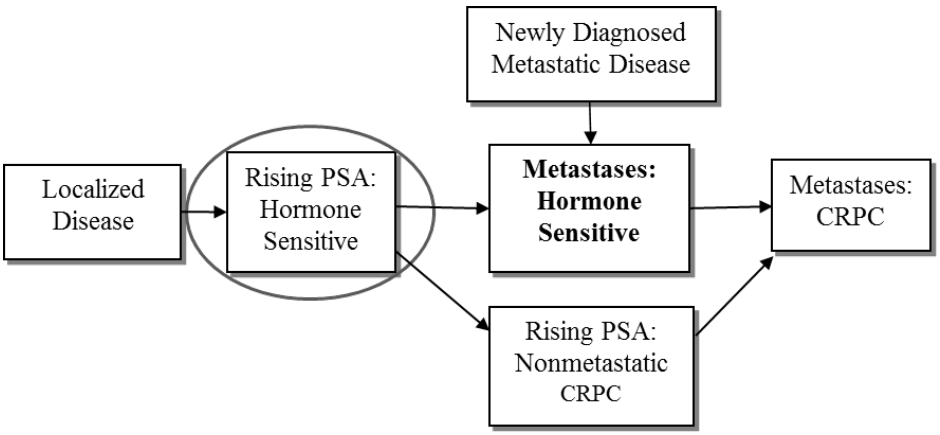
hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy (see section 5.1).

Epidemiology and risk factors, screening tools/prevention

Prostate cancer is the second most common diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 (Culp, M.B., et al Eur Urol, 2020). Within the EU, an estimated 473,344 new cases were diagnosed, and 108,088 men died of prostate cancer during 2020 [International Agency for Research on Cancer, 2020]. While prostate cancer remains the third leading cause of male cancer mortality in the EU (after lung and colorectal), the death rate has decreased in the EU by 7.1% from 2017 to 2022 and an estimated 69000 deaths due to prostate cancer were predicted for 2022 (Dalmartello M et al, Ann Oncol. 2022). In general, prostate cancer death rates have been decreasing since the early 1990s, which has been attributed to improvements in detection and treatment; however, the pace of decline in cancer death rates appears to have stabilized from 2013 to 2015.

Most cases present at an early stage and often have an indolent course. However, less than 10% of cases will have metastatic disease onset and it is estimated that up to one third of patients will develop eventual metastatic disease at some point of their disease course. Prostate cancer progresses through a series of characteristic clinical states that represent both the natural history of the disease and response to treatment (Scher HI et al, Urology. 2000), from initial diagnosis of either localized or metastatic disease that can then progress with rising PSA levels to metastatic hormone-sensitive disease or to nmCRPC, ultimately leading to mCRPC [Figure 1]. Early in the disease, prostate cancer cells need normal levels of androgens to survive. Such prostate cancers are referred to as androgen-dependent or hormone-sensitive; therefore, treatments that decrease androgen levels or block androgen activity can inhibit the growth of prostate cancer, and ADT is often initiated in men who experience recurrence or progression of their disease.

Figure 1 Model of Prostate Cancer Progression



CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen.

Source: modified from Scher & Heller [2000]

Clinical presentation, diagnosis and stage/prognosis

Following the initial evaluation and diagnosis of prostate cancer, the vast majority of men undergo primary localized treatment with curative intent (Marhold M et al, Cancer Lett. 2022; Buglione M et al, PLoS One. 2019; Hager B et al, Prostate Cancer Prostatic Dis. 2017; Cooperberg MR et al, J Clin Oncol. 2010). Of those, approximately one-third experience rising PSA or BCR within 10 years after primary therapy (Ward JF et al, Nat Clin Pract Urol. 2005; Han M, Partin AW et al, Urol Clin North Am. 2001) which

is commonly defined as PSA level > 0.2 ng/mL with a secondary confirmatory level above 0.2 ng/mL following prostatectomy or increase in PSA by ≥ 2 ng/mL above the nadir following radiation (Punnen S et al, Eur Urol. 2013). This rise in PSA uniformly represents recurrence of prostate cancer, the likely presence of micrometastatic disease and an increased risk of morbidity and mortality from prostate cancer (Pound CR et al, JAMA. 1999; Deguchi T et al, Br J Cancer. 1997).

Although a majority (>70%) of men with BCR after primary therapy do not develop metastases or die from prostate cancer, a subset of patients with rising PSA following primary therapy will develop clinically apparent metastases and will die as a result of the disease (Antonarakis ES et al, BJU Int. 2012; [1]Freedland SJ et al, JAMA. 2005; Freedland SJ et al, J Clin Oncol. 2007; Ward JF et al, Nat Clin Pract Urol. 2005; Punnen S et al, Eur Urol. 2013). Several parameters (e.g., prostate-specific androgen doubling time (PSADT) and Gleason score) have been studied to distinguish men who are likely to develop "clinically significant" disease from those who have more indolent disease after biochemical relapse. The PSADT is predictive of both clinical MFS and prostate cancer-specific mortality in men with a rising serum PSA after radical prostatectomy (Ward JF et al, Nat Clin Pract Urol. 2005; Freedland SJ et al, JAMA. 2005; Zhou P et al, J Clin Oncol. 2005; D'Amico AV et al, J Natl Cancer Inst. 2003). In addition, observational data from Johns Hopkins Universtity suggests that patients with biochemical relapse after radical prostatectomy who were at most risk for the development early metastases and death from prostate cancer had a Gleason score of 8 to 10 and a PSADT < 10 months (Han M et al, Urol Clin North Am. 2001; Punnen S et al, Eur Urol. 2013). In an analysis of 2 independent patient cohorts with biochemical relapse after surgery and PSADT < 12 months, predictors of MFS were identified (Markowski MC et al, Clin Genitourin Cancer. 2019). Results of this multivariate regression analysis suggest that the addition of absolute PSA level can better define an "at-risk" population identifying PSADT ≤ 7.5 months, PSA ≥ 0.5 ng/mL and Gleason score as independent predictors of MFS by multivariable analysis Pienta KJ et al, Clin Cancer Res. 2006).

Management

Monitoring PSA levels after definitive treatment of localized prostate cancer with either radiation therapy or radical prostatectomy leads to the identification of patients with PSA-only biochemical recurrence (Punnen S et al, Eur Urol. 2013). The diagnosis of BCR usually leads to radiological investigation to determine if the recurrence is localized to the prostate gland or the site from where it has been removed from, or metastatic. For patients with BCR in whom there is a significant likelihood that the disease is confined to the prostate or prostatic bed, local salvage therapy (for example, salvage prostatectomy, radiation therapy, brachytherapy or high-intensity focused ultrasound) may result in prolonged disease-free survival (Fossati N. et al, Eur Urol. 2016). If metastases are detected, these patients are treated as mHSPC. When increases in serum PSA are not accompanied by signs, symptoms or radiographic evidence of locally recurrent or disseminated disease and, testosterone levels are > 50 ng/mL, the underlying disease is generally hormone-sensitive and responsive to conventional ADT with gonadotropin-releasing hormone (GnRH) agonist, GnRH antagonist or orchiectomy. Systemic therapy with conventional ADT has been the primary therapeutic approach for patients in whom the rise in PSA is not accompanied by symptoms or radiographic evidence of disseminated disease and for those who have had local salvage therapy following their initial definitive treatment but who subsequently have a BCR with non-castrate serum levels of testosterone. Immediate, rather than deferred, ADT is recommended for most patients with BCR and the presence of high-risk features for early metastasis (i.e., PSADT < 10 months, Gleason score of 8 to 10) (Virgo KS et al, J Clin Oncol. 2021).

ADT or salvage local therapy is often used early after definitive therapy in patients with nmCSPC with high-risk BCR. Even with available prognostic factors, no therapies are approved for high-risk nmCSPC with evidence of disease recurrence by PSA but without overt metastases. ADT is administered to slow

the growth of prostate cancer, although there is evidence to suggest that ADT alone may not provide sustained long-term efficacy. After 5 years of treatment with ADT, approximately 10% to 20% of nmCSPC cases will develop into CRPC, defined by rising PSA levels or radiographic disease progression despite androgen suppression (Kirby M et al, J Med Econ. 2010; Alemayehu Bet al, J Med Econ. 2010; Cabrera C et al, Pharmacoepidemiol Drug Saf. 2010). An estimated 33% of patients with nmCRPC were found to develop distant metastases within 2 years of resistance. Despite low or undetectable levels of androgen in such patients, evidence suggests that AR signalling remains active and that their tumours continue to respond to therapies directed at the AR signalling axis (Pienta KJ et al, Clin Cancer Res. 2006).

Currently, no novel hormone therapies are approved in the EU or US for nmCSPC and the available treatment options such as ADT for these patients, notably those with high-risk nmPC, have limitations. The primary goal of treatment for this condition is to delay or decrease the risk of developing metastasis and emergence of castration-resistant disease and to prolong OS. Enzalutamide, which has demonstrated efficacy in other prostate cancer disease states, has the potential to address this unmet medical need in patients with nmCSPC with high-risk BCR.

Intermittent ADT has been proposed as an alternative to continuous ADT for treatment of advanced HSPC, since many of the acute and chronic side effects of ADT are due to castrate levels of testosterone. Periods of time when men are off therapy may be associated with decreases in these side effects, especially those associated with physical and sexual function, thereby improving quality of life. Intermittent ADT typically involves treatment for either a fixed interval of time or until a maximal response is achieved based upon PSA levels. ADT is then withdrawn, and patients are followed for evidence of recurrence. As testosterone production resumes, the side effects of ADT are mitigated, but the risk of disease progression also increases. The patient is followed with PSA measurements, and ADT is reinitiated based on a predefined threshold level of serum PSA. Multiple randomized trials and meta-analysis have addressed the benefit of intermittent androgen deprivation regarding improvements in physical function and quality of life, although questions remain as to the survival impact of intermittent therapy (Pienta KJ et al, Aging Male. 2015; Botrel TEA et al, BMC Urol. 2014; Brungs D, et al, Prostate Cancer Prostatic Dis. 2014; Niraula S et al, J Clin Oncol. 2013; Tsai H-T et al, Urology. 2013).

2.1.2. About the product

Enzalutamide is an AR inhibitor that targets the AR signal pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity (see SmPC section 5.1).

Enzalutamide was first approved in the EU in June 2013 for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel. The indication for enzalutamide was subsequently extended to include all patients with mCRPC in November 2014. Enzalutamide has also been approved for the treatment of patients with non-metastatic castration-resistant prostate cancer in October 2018 and later, in April 2021, enzalutamide was approved for the treatment of patients with metastatic castration-sensitive cancer (mCSPC), also referred to as metastatic hormone-sensitive prostate cancer (mHSPC).

The MAH applied for an extension of indication for Xtandi as follows: "*as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high risk biochemical recurrent*

(BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy (see section 5.1).

The recommended dose is 160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice.

The MAH received prior scientific advice (EMEA/H/SA/1612/1/FU/2/2012/III) in January 2013. Questions were included on the acceptability of the design of a new phase 3 trial of enzalutamide added on to GnRH analogue therapy in males with high-risk prostate cancer that is progressing following definitive therapy. The CHMP recommended conducting two separate studies that resulted in dividing the protocol into the studies EMBARK (in nmHSPC) and ARCHES (in mHSPC). The content of this advice included discussion about the primary and secondary endpoints, frequency of imaging, comparator treatment, main inclusion/exclusion criteria and definition of high risk.

2.1.4. General comments on compliance with GCP

The MAH claims that the clinical trials were performed in accordance with Good Clinical Practice standards. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. The nonclinical pharmacology, pharmacokinetics and toxicology enzalutamide have been well characterized in a full non-clinical packaged included in the original MAA for Xtandi. However, an updated Environmental Risk Assessment (ERA) has been submitted as part of this application for an extension of the indication.

2.2.1. Introduction

The purpose of this submission is to extend the current Marketing Authorization for Xtandi to include patients with non-metastatic hormone-sensitive prostate cancer (nmHSPC) with high-risk biochemical recurrence (BCR). Therefore, an updated environmental risk assessment report for enzalutamide has been provided in accordance with the EMA guidelines. This re-assessment report considers the potential impact of the increased patient population from the new indication on the environmental risk assessment of enzalutamide.

2.2.2. Ecotoxicity/environmental risk assessment

An updated environmental risk assessment report for enzalutamide has been submitted in accordance with the 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use' (EMA/CHMP/SWP/4447/00 corr. 2[1*,] EMA 2006) and the 'Questions and answers on the Guideline' (EMA/CHMP/SWP/44609/2010 Rev. 1, EMA, adopted 26 May 2016). The main studies results are summarised below.

Table 1. Report providing relevant endpoints of the environmental risk assessment of Enzalutamide

Substance (INN/Invented Name): Enzalutamide			
CAS-number: 915087-33-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.99	Not potential PBT
PBT assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Considered to be<2000 L/kg	Not B
Persistence	DT50	> 180 days fresh sediment (12°C)	vP
Toxicity	NOEC	No toxicity in the aquatic compartment.	Not T
PBT-statement	The compound is not considered as BT nor vB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.0047	μg/L	< 0.01 threshold: Not
Other concerns			Potential endocrine disruptor
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc = 436 (sandy loam) Koc = 612 (clay loam) Koc = 238 (clay loam) Koc = 945 (sludge) Koc = 870 (sludge)	No terrestrial studies triggered
Ready Biodegradability Test	OECD 301	Not conducted	Considered not readily biodegradable

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} water = 44.9 and 53 d DT_{50} total = 515and 421 d % shifting to sediment (103 days): 57.5% and 51.9 % (enzalutamide); 75.8% and 68.7 % (total radioactivity)			Transformation product (19.5% in total system): 4 - (3 - [4 - cyano - 3 - (trifluoromethyl) phenyl] - 5,5 - dimethyl - 2,4 - dioxoimidazolidin - 1 - yl) - 2 - fluoro - N - ethylbenzamide
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	1370	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	318	µg/L	Live neonates
Fish, Eary Life Stage Toxicity Test	OECD 210	NOEC	971	µg/L	All paramenters
Fish, Sexual Development Test		NOEC	890	µg/L	All paramenters
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	$1x10^6$	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305				
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC	82.1	mg/kg dry weight	NOEC recalculated for standard sediment (containing 10% organic carbon)

2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable

An environmental risk assessment (ERA) has been submitted in accordance with the current *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/4447/00 corr 2^{1*}). The predicted environmental concentration (PEC) for enzalutamide is 0.047 µg/L which exceeds the trigger value of 0.01 µg/L as given by EMEA (2006) and therefore an environmental assessment Phase II–Tier A was performed.

Enzalutamide has a partition coefficient lower than 4.5 (log K_{ow} = 2.99 at pH= 7). A further PBT assessment is not warranted. However, since enzalutamide is not considered biodegradable, the MAH performed a Tier B assessment.

According to the current EMEA Guidance document, since the PEC/PNEC and the PEC/PNEC microorganism are less than 1, no further aquatic tests or tests with microorganisms are required.

Enzalutamide is unlikely to exhibit a BCF > 2000 L/kg and is therefore considered not to bioaccumulate in fish.

Since the $PEC_{SEDIMENT}/PNEC_{SEDIMENT}$ is less than 1, no further testing on sediment dwelling organisms is required. It is unlikely that there is a risk to sediment dwelling organisms from enzalutamide.

Tier B terrestrial risk assessment is not triggered because of the low absorption of enzalutamide to sewage sludge. Therefore, enzalutamide is unlikely to represent a risk to the aquatic or terrestrial environments.

2.2.4. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of enzalutamide.

Considering the above data, enzalutamide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study/ Protocol Number/Title	**Status**	**Study Design**	**Primary Endpoint Analysis**	**Treatment Dose/ Number of Participants**
Phase 3				

Study/ Protocol Number/Title	Status	Study Design	Primary Endpoint Analysis	Treatment Dose/ Number of Participants
C3431004/EMBARK MDV3100-13/ Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High Risk Nonmetastatic Prostate Cancer Progressing After Definitive Therapy	Study Start: 17 December 2014 PCD 31 Jan 2023	Phase 3, randomized, double-blind, placebo-controlled study of enzalutamide plus leuprolide, open-label enzalutamide monotherapy, and placebo plus leuprolide in patients with high risk nonmetastatic castration-sensitive prostate cancer progressing after radical prostatectomy or radiotherapy or both. All patients had a PSADT ≤ 9 months. No prior cytotoxic chemotherapy or ADT (with exceptions) was allowed.	MFS†	• 355 patients in enzalutamide 160 mg/day (4 capsules of 40 mg each) plus leuprolide 22.5 mg for 3 months (22.5 mg injection once every 12 weeks formulated for either intramuscular or subcutaneous) • 355 patients in enzalutamide monotherapy 160 mg/day (4 capsules of 40 mg each). • 358 patients in placebo (capsules identical in appearance to enzalutamide capsules, were administered in the same manner as enzalutamide) plus leuprolide 22.5 mg for 3 months (22.5 mg injection once every 12 weeks formulated for either intramuscular or subcutaneous)

2.3.2. Clinical pharmacology

No new pharmacology data were submitted in support of this application.

2.3.1. Discussion and conclusion on clinical pharmacology

No additional data have been provided with this submission which is considered acceptable as the clinical pharmacology properties of enzalutamide were described in detail in the original marketing application and previous procedures with new clinical data consistent with results in the original marketing authorisation application. The study included in support of this application used enzalutamide at the approved dose of 160 mg/day, which has been established as a generally safe and efficacious dose in patients with CRPC and mHSPC.

2.4. Clinical efficacy

2.4.1. Dose response study

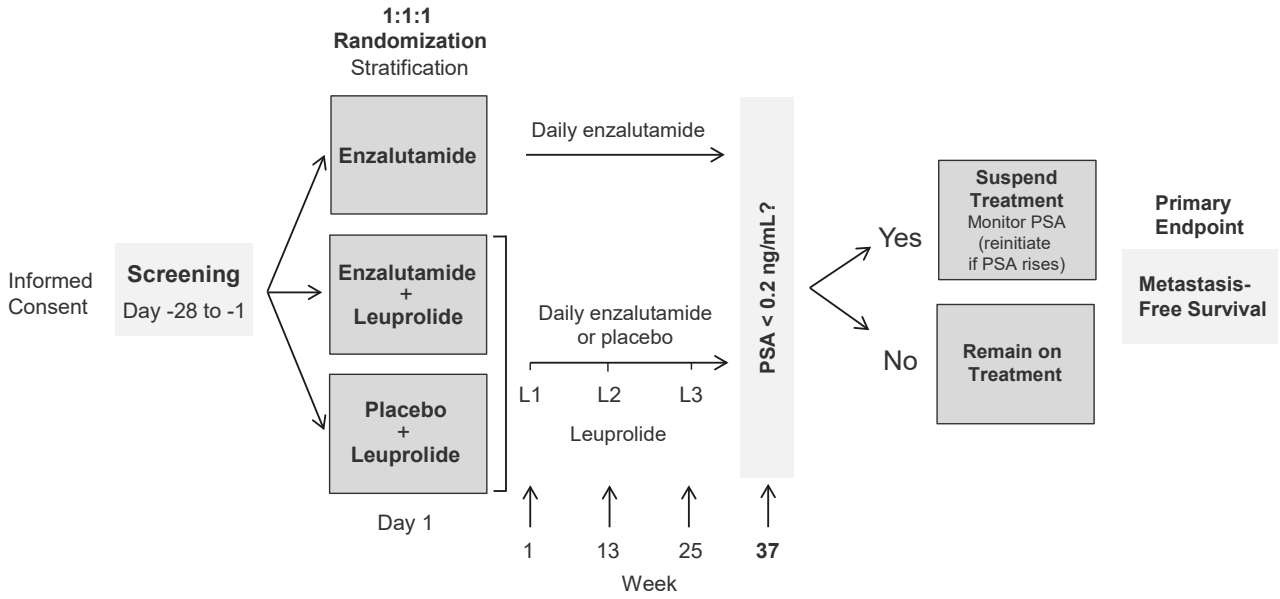
No new dose responses studies were submitted with this application. The posology for the proposed indication (enzalutamide 160 mg administered orally once daily) is the daily dose authorised for other indications.

2.4.2. Main study

Study MDV3100-13 (EMBARK)

A Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men with High Risk Non-metastatic Prostate Cancer Progressing After Definitive Therapy.

Figure 2. Study schematic



Primary Assessment: Radiographic imaging approximately every 6 months

This efficacy section presents the primary, secondary, and exploratory endpoints of EMBARK based on a cut-off date of 31 Jan 2023.

Methods

Study participants

Eligibility criteria were chosen to include patients with hormone sensitive high risk non-metastatic prostate cancer progressing after definitive therapy and were at high risk of developing metastases. High risk prostate cancer was defined in this study as biochemical recurrence with a PSADT ≤9 months and screening PSA by the central laboratory of ≥1 ng/mL for patients who had prior radical prostatectomy (with or without radiotherapy) and at least 2 ng/mL above the nadir for patients who had prior primary radiotherapy only.

Inclusion criteria

1. Age 18 years or older and willing and able to provide informed consent.
2. Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features.
3. Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. Prostate cryoablation is not considered definitive therapy for this study, but its prior use is not exclusionary.
4. PSA doubling time ≤9 months as calculated by the sponsor (*Arlen PM, Bianco F, Dahut WL, D'Amico A, Figg WD, Freedland SJ, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. J Urol. 2008 Jun;179(6):2181-6*).
5. Screening PSA by the central laboratory ≥1 ng/mL for patients who had radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer and at least 2 ng/mL above the nadir for patients who had radiotherapy only as primary treatment for prostate cancer.
6. Serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening.
7. ECOG performance status of 0 or 1 at screening.
8. Estimated life expectancy of ≥12 months.
9. Able to swallow the study drug and comply with study requirements.
10. Throughout the study, the patient and his female partner who was of childbearing potential must have used 2 acceptable methods of birth control (1 of which must include a condom as a barrier method of contraception) from screening through 3 months after the last dose of study drug or per local guidelines where these require additional description of contraceptive methods.
11. Throughout the study, the patient must have used a condom if having sex with a pregnant woman.
12. Must have agreed not to donate sperm from first dose of study drug through 3 months after the last dose of study drug.

Exclusion criteria

1. Prior or present evidence of distant metastatic disease as assessed by computed tomography (CT) or magnetic resonance imaging (MRI) or chest x-ray for soft tissue disease and whole-body radionuclide bone scan for bone disease. Patients with soft tissue pelvic disease could be eligible if the short axis of the largest lymph node is <20 mm for lymph nodes below aortic bifurcation. If the screening bone scan showed a lesion suggestive of metastatic disease, the patient would have been eligible only if a second imaging modality (plain film, CT, or MRI) didn't not show bone metastasis. If the imaging results were equivocal or consistent with metastasis by central radiology review, the patient was not eligible for enrolment. Positron-emission tomography (PET) was not an evaluable imaging modality for this study.
2. Prior hormonal therapy. Neoadjuvant/adjuvant therapy to treat prostate cancer ≤36 months in duration and ≥9 months before randomization, or a single dose or a short course (≤6 months) of hormonal therapy given for rising PSA ≥9 months before randomization was allowed.
3. Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for prostate cancer.
4. Prior systemic biologic therapy, including immunotherapy, for prostate cancer.

5. Major surgery within 4 weeks before randomization date.
6. Treatment with 5-α reductase inhibitors (finasteride, dutasteride) within 4 weeks of randomization.
7. For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator in consideration of appropriate guidelines (eg, American Society for Radiation Oncology/American Urological Association [ASTRO/AUA]; European Association of Urology [EAU]).
8. Participation in a clinical study of an investigational agent that inhibits the androgen receptor or androgen synthesis (eg, TAK-700, ARN-509, ODM-201); patients who received placebo were allowed.
9. Use of any other investigational agent within 4 weeks before randomization date.
10. Known or suspected brain metastasis or active leptomeningeal disease.
11. History of another invasive cancer within 3 years before screening, with the exception of fully treated cancers with a remote probability of recurrence. The medical monitor and investigator must have agreed that the possibility of recurrence was remote.
12. Absolute neutrophil <1500/μL, platelet count <100,000/μL, or hemoglobin <10 g/dL (6.2 mmol/L) at screening. NOTE: May not have received any growth factors or blood transfusions within 7 days before the hematology values obtained at screening.
13. Total bilirubin (TBili) ≥1.5-times the upper limit of normal (except patients with documented Gilbert's disease), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5-times the upper limit of normal at screening.
14. Creatinine >2 mg/dL (177 μmol/L) at screening.
15. Albumin <3.0 g/dL (30 g/L) at screening.
16. History of seizure or any condition that may predispose to seizure (eg, prior cortical stroke or significant brain trauma). History of loss of consciousness (unless of cardiac origin) or transient ischemic attack within 12 months before randomization.
17. Clinically significant cardiovascular disease including different criteria.
18. Gastrointestinal disorder affecting absorption.
19. Hypersensitivity reaction to enzalutamide or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene.
20. Contraindication to the use of leuprolide, such as a previous hypersensitivity reaction to an LHRH analogue or any of the excipients in the leuprolide injection.
21. Ongoing drug or alcohol abuse as per investigator judgment.

Treatments

Patients received either enzalutamide plus leuprolide, enzalutamide monotherapy or placebo plus leuprolide therapy based on randomization.

Enzalutamide was administered at the authorised dose of 160 mg/day (four 40 mg capsules) with or without food.

Leuprolide acetate (leuprorelin acetate) 22.5 mg was given as a single intramuscular or subcutaneous injection once every 12 weeks (for a minimum of 3 doses, providing 36 weeks of treatment).

Placebo capsules, identical in appearance to enzalutamide capsules, were administered in the same manner as enzalutamide.

PSA was monitored throughout the study. Study treatment was to continue uninterrupted in the absence of disease progression until the central laboratory PSA evaluation at Week 36. At Week 37, study treatment was suspended for participants whose PSA values were undetectable (<0.2 ng/mL) at Week 36 as determined by the central laboratory; PSA and testosterone were measured every 3 months thereafter by the central laboratory.

Based on the latest protocol version (Amendment 4, dated 29 Oct 2021), beginning 22 Feb 2019, investigators started to be notified when any of their patients develop protocol defined PSA progression with a PSA doubling time (PSADT) ≤10 months while on study treatment based on central laboratory assessments. This notification was put in place following the approval of Xtandi (enzalutamide) and apalutamide for the treatment of patients with non-metastatic (M0) CRPC in men with high-risk prostate cancer, based on studies which demonstrated that treatment with Xtandi plus ADT or apalutamide plus ADT conferred significant improvement in the primary endpoint of MFS versus ADT alone. Given this, patients participating in EMBARK study who developed non-metastatic (M0) CRPC were eligible to receive an approved treatment for M0 CRPC

Objectives

The objective of this study was to evaluate the efficacy and safety of enzalutamide plus leuprolide and enzalutamide monotherapy versus placebo plus leuprolide in patients with high-risk BCR.

Primary objective

To evaluate efficacy of the combination of enzalutamide plus leuprolide versus placebo plus leuprolide, as measured by metastasis-free survival (MFS).

Secondary objectives

To evaluate efficacy as measured by the following key secondary endpoints:

- MFS between enzalutamide monotherapy versus placebo plus leuprolide.
- Time to PSA progression
- Time to first use of new antineoplastic therapy
- Overall survival

Other secondary endpoints:

- Time to distant metastasis;
- Proportion of patients per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA;
- Proportion of patients per group with undetectable PSA at 36 weeks on study drug;
- Time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA;

- Time to first symptomatic skeletal event;
- Time to castration resistance;
- Time to symptomatic progression;
- Time to clinically relevant pain;
- Quality of life;
- Safety.

Exploratory objective/endpoint

- Progression-free survival on first subsequent therapy (PFS2)

Outcomes/endpoints

An overview of the study endpoints and statistical analyses are presented in table 1.

Table 2. EMBARK Primary, Secondary, and Exploratory Endpoints and Analyses – ITT Population

Endpoint	Description	Analyses
Primary Endpoint		
MFS betwen combination of enzalutamide plus leuprolide versus placebo plus leuprolide	BICR assessed by radiographic progression per RECIST 1.1 (soft tissue disease) and radiographic progression for the appearance of 1 or more metastatic lesion (bone disease) in patients with nmCSPC	– HR (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.1.1)
Key Secondary Endpoint		
MFS between enzalutamide monotherapy versus placebo plus leuprolide	BICR assessed by radiographic progression per RECIST 1.1 (soft tissue disease) and radiographic progression for the appearance of 1 or more metastatic lesion (bone disease) in patients with nmCSPC	– HR (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.2.1)
Time to PSA progression	Time to PSA progression	– Time to event (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.2.2)
Time to first use of new antineoplastic therapy	Time to first use of new antineoplastic therapy after study drugs discontinuation	– Time to first use (2-sided stratified log rank test) (SAP Section 6.2.3)

Endpoint	Description	Analyses
OS	Time to death due to any cause based on an interim analysis. Final OS data will be provided after 271 deaths have occurred across the 3 treatment arms.	– HR (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) – Survival rates (SAP Section 6.2.4)
Other Secondary Endpoints		
Time to distant metastasis	Duration in months from randomization to the earliest objective evidence of distant soft tissue metastases or metastatic bone disease by BICR	– HR (2-sided stratified log rank test) (SAP Section 6.3.1)
Proportion of patients per group who remain treatment free 2 years after suspension of study treatment at week 37 due to undetectable PSA	Proportion of patients per group who remain treatment free 2 years after suspension of study treatment at week 37 due to undetectable PSA compared between treatment groups using the stratified Cochran Mantel Haenszel test	– Stratified Cochran Mantel Haenszel test (SAP Section 6.3.2)
Proportion of patients per group with undetectable PSA 2 years after suspension of study treatment at week 37 due to undetectable PSA	The proportion of patients per group with undetectable PSA 2 years after suspension of study treatment at week 37 due to undetectable PSA compared between treatment groups	– Stratified Cochran Mantel Haenszel test (SAP Section 6.3.3)
Proportion of patients per group with undetectable PSA at 36 weeks on study drug	The proportion of patients per group with undetectable PSA at 36 weeks compared between treatment groups	– Stratified Cochran Mantel Haenszel test (SAP Section 6.3.4)
Time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA	Duration in months between the date of treatment suspension at week 37 due to undetectable PSA and the date that hormonal therapy is restarted	– Time to event (2-sided stratified log rank test) (SAP Section 6.3.5)
Time to castration resistance	Applies only to patients receiving leuprolide treatment. Duration in months to disease progression (BICR, PSA) or symptomatic skeletal event (< 50 ng/dL testosterone levels)	– Time to event (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.3.6)

Endpoint	Description	Analyses
Time to symptomatic progression	Time to first symptomatic skeletal event	– Time to event (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.3.7; 6.3.8)
PROs Pain QoL	Time to clinically relevant pain progression from randomization to onset of pain progression – patient-reported pain symptoms per BPI-SF Time to a 10-point decline (deterioration) in global FACT-P score – patient-reported global health status/QoL, functioning, and symptoms per FACT-P, EQ-5D-5L, and QLQ-PR25 questionnaires	– Descriptive statistics – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.4)
Exploratory Endpoint		
PFS2	PFS2 the time in months from date of randomization to date of investigator-determined disease progression (PSA progression, progression on imaging, or clinical progression) or death due to any cause, whichever occurred first, while the patient was receiving first subsequent therapy for prostate cancer	– HR (2-sided stratified log rank test) – Kaplan-Meier estimates of medians (2-sided 95% CI) (SAP Section 6.5)

Sample size

The following assumptions were used to determine sample size calculation for the MFS endpoint for the primary and key secondary analysis:

- Overall 2-sided Type I error rate: 0.05
- Randomization: 1:1:1
- Median MFS for the control group: 55 months

An observed 142 MFS events in the 2 blinded treatment groups would have provide approximately 90% power to detect a target hazard ratio of 0.58 using a 2-sided log-rank test with a 0.05 level of significance. This target hazard ratio corresponds to a difference of approximately 40 months in median MFS assuming an exponential distribution for MFS and a constant hazard rate for each group. For the key secondary hypothesis of MFS for the monotherapy arm, the target effect size, and expected number of MFS events were the same as the primary hypothesis in the combination arm. As a 2-sided alpha of 0.03

would have been utilized for the monotherapy comparison, the power for this analysis was to be 86% with 142 MFS events observed. At the time of the final analysis, at least 197 MFS events total were expected for the 3 treatment groups. The study would have required approximately 1050 patients (350 in each group) to achieve the 197 MFS events across the 3 treatment arms. This sample size calculation accounted for a 5% loss to follow-up by the end of 4 years for all 3 treatment groups.

An actual enrolment of 1068 patients would have also allowed for an assessment for the key secondary endpoint of OS.

Randomisation

A central randomization of 1:1:1 was used to assign patients to one of the following study treatments:

- Enzalutamide 160 mg/day plus leuprolide 22.5 mg IM/SC every 3 months;
- Enzalutamide monotherapy 160 mg/day;
- Placebo (capsules identical in appearance to enzalutamide capsules, were administered in the same manner as enzalutamide) plus leuprolide 22.5 mg IM/SC every 3 months.

Randomization was stratified by the following, as recorded in the Interactive Response Technology (IRT):

- Screening PSA ≤10 ng/mL vs >10 ng/mL
- PSA doubling time ≤3 months vs > 3 to ≤9 months
- Prior hormonal therapy vs no prior hormonal therapy

Unless otherwise specified, stratified analyses utilized strata as defined in the randomization system.

Blinding (masking)

Treatment with enzalutamide monotherapy was open-label. Treatment with enzalutamide plus leuprolide and placebo plus leuprolide was double blinded.

All patients, study site personnel (including investigators), and sponsor staff and its representatives were blinded to enzalutamide or placebo treatment assignment when administered in combination with leuprolide. The blinded control for enzalutamide were placebo capsules identical in appearance to the enzalutamide capsules.

Statistical methods

Analysis populations

Based on the SAP version 3.1, dated on 10-Jan-2023, the following analysis populations were defined:

The intent-to-treat population (ITT) was defined as all patients randomly assigned to study treatment. The intent-to-treat population was used for all efficacy analyses unless otherwise specified, and was analysed based on randomized treatment assignment.

The evaluable ITT (eITT) population was defined as all patients in the ITT population who have confirmed non-metastatic disease at baseline by independent central radiology review. This analysis population was to be used for certain efficacy analyses as specified in the statistical analysis plan.

The safety population was defined as all patients who receive any amount of study drug. The safety population was to be used for all safety analyses. The safety population was to be analysed based on the treatment received and not the treatment assigned.

Primary endpoint: MFS

The primary efficacy analysis compared MFS based on BICR assessment between enzalutamide in combination with leuprolide versus placebo in combination with leuprolide using a 2-sided stratified log-rank test. The primary population for analysis was the ITT population. Strata were to be based on those specified in the randomization system.

For patients not known to have had radiographic progression and who have not died at the time of the analysis data cut-off, MFS time would have been censored at the date of the last adequate assessment on or before the analysis data cut-off date. For patients who were randomized but later confirmed to have metastatic disease at enrolment or who had no adequate post-baseline tumour assessment, information would have been censored on the date of randomization.

The censoring rules for the primary and sensitivity analyses of MFS are summarized in Table 3.

Table 3 . Censoring Rules for the Primary and Sensitivity Analyses of MFS

Analysis	Censoring Rules	Date of Censoring
Primary analysis of MFS	Patients with no baseline or no post baseline assessments who have not died within 49 weeks after randomization	Date of randomization
	Patients who were randomized but confirmed metastatic at baseline	Date of randomization
	Patients who had no confirmed metastasis and did not die prior to data cutoff date	Date of the last adequate radiographic tumor assessment prior to data cutoff date
	Patients who initiate antineoplastic therapy such as cytotoxic chemotherapy, abiraterone acetate, hormonal agents, prostate cancer vaccines, nonradioactive bone-targeting agents and systemic radiopharmaceuticals for prostate cancer, or any antineoplastic therapy without evidence of metastasis	Date of the last adequate radiographic tumor assessment prior to first use of any such therapy
	Patients with radiation therapy performed for prostate cancer-related lesions without evidence of metastasis	Date of the last adequate radiographic tumor assessment prior to the earliest use of radiation therapy
	Patients with evidence of metastasis or death after 2 or more consecutive missed tumor assessment visits	Date of the last adequate radiographic tumor assessment prior to the first missed visit date

MFS = Metastatic Free Survival; of note, the censoring rules are applied to MFS events by either radiographic progression, or death due to any cause without evidence of radiographic progression; of note, antineoplastic therapies according to the above search criteria undergo medical review to confirm.

Sensitivity/Robustness Analyses

The following sensitivity analyses were to be performed for MFS.

- Sensitivity 1: Including Events Regardless of Initiation of Antineoplastic Therapies

Censoring rules were to follow those in the primary MFS analysis except that events occurring for the first time after the initiation of antineoplastic therapy would not be censored and be considered as events. A 2-sided stratified log-rank test (same as the primary analysis) would have been used to compare the treatment groups.

- Sensitivity 2: MFS on eITT Population

MFS for the eITT population was also to be analysed as a sensitivity analysis. The definition of MFS and censoring rules was to be consistent with primary analysis. A 2-sided stratified log-rank test was to be used to compare the treatment groups. All methods from the primary efficacy analysis would have been repeated.

- Sensitivity 3: MFS Based on Investigator Assessment

MFS as assessed by the investigator was also to be analysed as a sensitivity analysis.

The definition of MFS and censoring rule were to be consistent with primary analysis. A 2-sided stratified log-rank test was to be used to analyse the MFS values. Furthermore, the concordance and discordance rates between the independent central radiology review and investigator assessment were to be summarized using the metastasis status by the treatment groups

- Sensitivity 4: Impact of Clinical Progression

In this sensitivity analysis, patients who discontinue study drug primarily due to clinical deterioration prior to protocol-defined evidence of radiographic progression were be considered as having clinical progression. For this analysis, MFS was defined as the duration of time between randomization and the earliest objective evidence of metastatic disease, date of study drug discontinuation for clinical progression, or death, or evidence of clinical progression, whichever occurred first. The censoring rules used for the primary analysis were to be utilized. The hazard ratio and its 95% confidence interval were to be reported.

- Sensitivity 5: Impact of Censoring Due to Discontinuation Prior to Radiographic Progression for Patients Notified of PSA Progression or Progression by Positron Emission Tomography (PET) Imaging of Prostate-specific Membrane Antigen (PSMA).

For the censoring of MFS for the patients who reached PSA progression and discontinued study treatment prior to the development of radiographically detectable metastatic disease, and the potential for this to be informative censoring, a reference-based imputation method based on Bayes Gibbs sampling as outlined by Lu, Li, and Koch (Lu et al. 2015) was to be implemented to assess the impact of the above censoring. If applicable, the inverse probability of censoring weighting (IPCW) method by Robins and Finkelstein could be used to adjust for the above censoring.

In order to assess the impact of patients initiating novel androgen inhibitors (such as enzalutamide, apalutamide, darolutamide and abiraterone) prior to the development of radiographically detectable metastatic disease, if applicable, the following sensitivity analyses could be performed: the Rank-Preserving Structural Failure Time Model (RPSFTM) (Robins & Tsiatis 1991), IPCW method (Robins & Finkelstein, 2000) and the two-stage method (Latimer & Abrams 2014).

Key secondary endpoints

<u>MFS (enzalutamide monotherapy vs. placebo plus leuprolide)</u>

MFS between enzalutamide monotherapy versus placebo plus leuprolide was to be defined as above for primary analysis of the combination comparison. Analysis of this endpoint was to be performed using the 2-sided stratified log-rank test to compare the 2 treatment groups with the same strata described above.

A Cox proportional hazards model was to be used to evaluate the MFS analysis to calculate the HR and its 95% CI.

The same sensitivity analyses as those specified for the primary comparison between enzalutamide in combination with leuprolide versus placebo in combination with leuprolide was to be implemented.

Time to PSA Progression

Only results from PSA samples taken before the initiation of any new prostate cancer therapy and after the start of study drug were to be considered.

PSA progression was defined as the date that a ≥25% increase and an absolute increase of ≥2 μg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline by week 25) that was confirmed by a second consecutive value at least 3 weeks later. The date of PSA progression was the first date the PSA progression was observed. For patients who have suspended treatment at week 37 and later reinitiated treatment, baseline was to be defined as the last PSA assessment prior to or on the date of reinitiation. The date of PSA progression was the first date the PSA progression was observed.

PSA progression was only defined during active study treatment; therefore, patients meeting PSA progression during the suspension period was to be censored unless the PSA progression criteria were subsequently met following treatment reinitiation. Time to PSA progression was to be censored on the date of the last PSA sample taken. Patients with PSA progression after 2 or more consecutive missed PSA assessments (ie, time interval >6 months or 182 days between 2 consecutive PSA samples) was to be censored on the date of last PSA assessment prior to the missed assessments. In patients with no baseline PSA and patients with no post-baseline PSA results, time to PSA progression was to be censored on the date of randomization.

Time to PSA progression was to be compared between treatment groups using a 2-sided stratified log-rank test.

Time to First Use of New Antineoplastic Therapy

New antineoplastic therapy included medications used specifically for prostate cancer treatment including hormonal treatments, immunotherapy, chemotherapy and investigative agents.

Time to first use of new antineoplastic therapy was to be compared between treatment groups using a 2-sided stratified log rank test. In patients with no new antineoplastic therapy initiated for prostate cancer after randomization, time to start of new antineoplastic therapy was to be censored on the last visit date or the date of randomization, whichever occurs last.

Overall Survival

The overall survival was to be compared between treatment groups using a 2-sided stratified log rank test. Patients without an event date was to be censored at the date of the last contact.

Decision rules

No interim analysis for the primary endpoint (MFS) were planned. The interim and final analyses for the key secondary endpoint OS were to be performed after the target number of events have occurred in the 3 treatment arms. A maximum of 2 distinct analysis cut-offs were planned according to the numbers of events described below:

- Final MFS and OS interim analyses at the time when 197 MFS events have occurred for the 3 treatment groups;
- Final OS analysis at the time when 271 deaths have occurred for the 3 treatment groups.

Table 4. MFS Based on Independent Review (2 Blinded Treatment Arms) – Efficacy Boundary

Analysis	Analysis Cut-Off Trigger	Number of MFS Events (2 Blinded Arms)[a]	Fraction of Required MFS Events	p-value (z-value) for Efficacy
Final MFS	197 MFS events in 3 arms	142	100%	≤0.05 (-1.9600)

MFS = metastasis-free survival
[a] Number of events expected for MFS in blinded treatment arms assuming a hazard ratio of 0.58.

Table 5. OS (2 Blinded Treatment Arms) – Efficacy Boundaries

Analysis	Analysis Cut-Off Trigger	Number of OS Events (2 Blinded Arms)[a]	Fraction of Required OS Events	p-value (z-value) for Efficacy[b]
IA OS	197 MFS events in 3 arms	82	43%	≤0.0001 (-3.89059)
Final OS	271 OS events in 3 arms	191	100%	≤0.04999 (-1.96001)

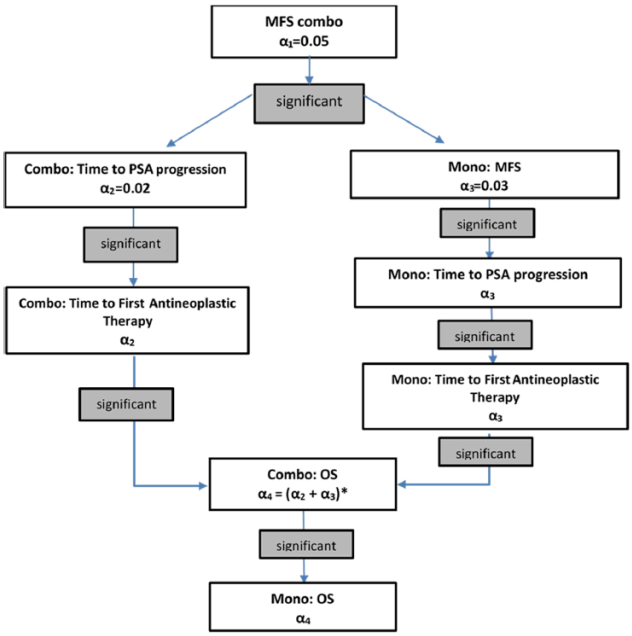
OS = overall survival; IA = interim analysis; MFS metastatic-free survival.
a. Number of events expected for OS in blinded treatment arms assuming a hazard ratio of 0.67.
b. The p-values and z-values noted for OS are those associated with the scenario where all the key secondary endpoints for the blinded treatment arms and the monotherapy arm are statistically significant (α=0.05).

Multiplicity adjustment for efficacy analysis

Alpha protected efficacy analyses included tests for the primary endpoint of MFS for enzalutamide plus leuprolide versus placebo plus leuprolide, and all 3 key secondary efficacy endpoints (time to PSA progression, time to first antineoplastic therapy, and overall survival) for the combination comparisons. Additionally, MFS, time to PSA progression, time to first antineoplastic therapy, and overall survival would have been tested for enzalutamide monotherapy versus placebo plus leuprolide.

If the test for the primary endpoint (MFS in the combination arms) was significant at the full 2-sided alpha level of 0.05, the key secondary endpoints for the combination arms was to be tested at a 2-sided alpha of 0.02 utilizing a hierarchical approach to preserve the family-wise Type I error rate. The remaining 0.03 alpha was to be allocated to compare MFS as well as other key secondary endpoints for enzalutamide monotherapy versus placebo plus leuprolide. The efficacy analyses and the multiplicity adjustment rules are summarized in **Figure 3**

Figure 3. Key efficacy analyses and multiplicity adjustment

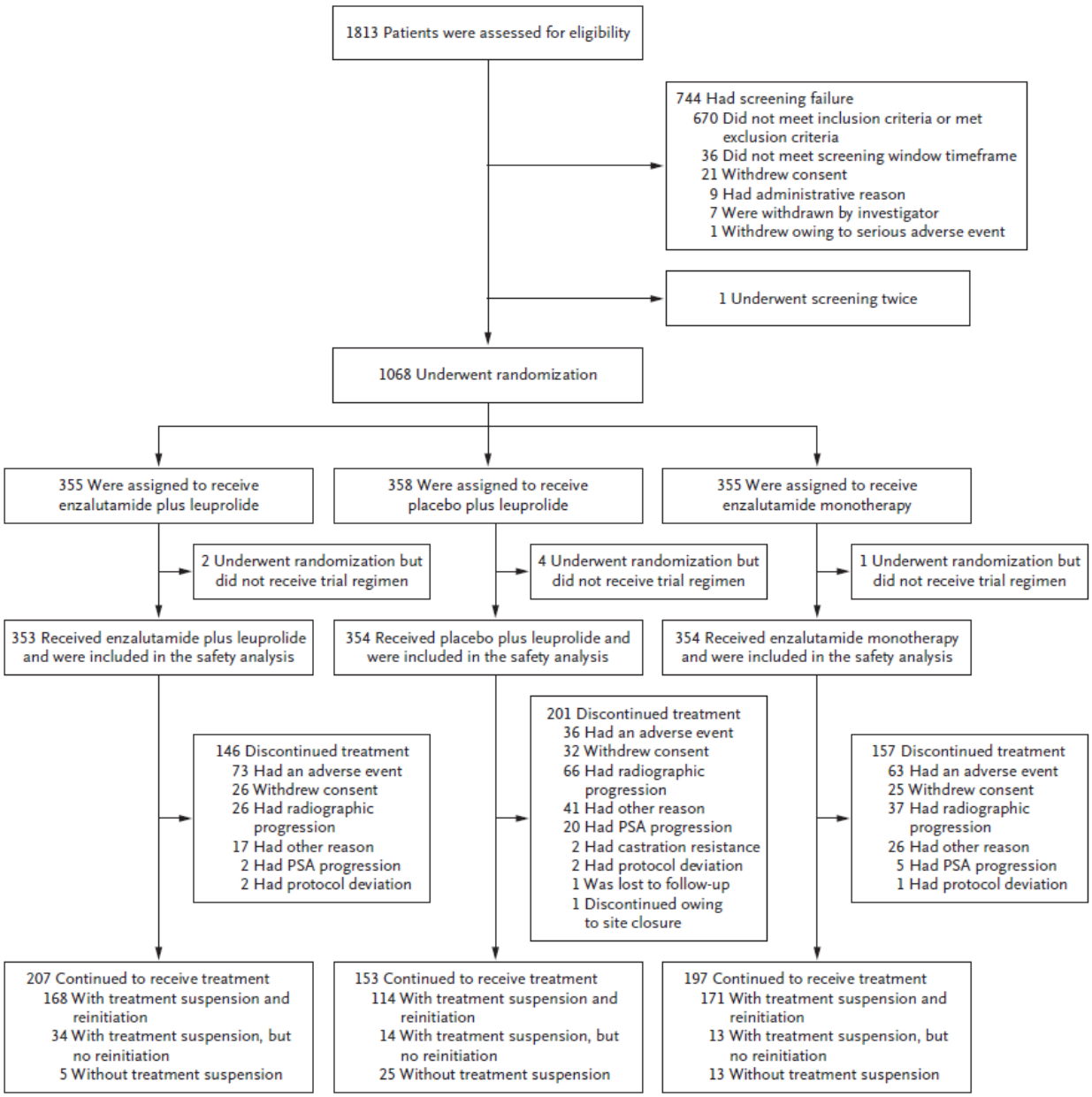


Source: Appendix 16.1.9.1, SAP Figure 2

Results

Participant flow

Figure 4. Participant disposition in the EMBARK Study



PSA: prostate-specific antigen.

Source: [Freedland et al, 2023]

Recruitment

Since December 2014, a total of 1068 participants were enrolled at 174 centres in 17 countries, including 55 centres in North America, 75 centres in Europe, and 44 centres in the rest of the world.

Table 6. Patient Disposition by Study Treatment Phase (ITT Population)

	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
Study Treatment Phase Disposition				
Ongoing	207 (58.3%)	153 (42.7%)	197 (55.5%)	557 (52.2%)
Patients with Treatment Reinitiation	168 (47.3%)	114 (31.8%)	171 (48.2%)	453 (42.4%)
Patients with Treatment Suspension but no Reinitiation	34 (9.6%)	14 (3.9%)	13 (3.7%)	61 (5.7%)
Patients without Treatment Suspension	5 (1.4%)	25 (7.0%)	13 (3.7%)	43 (4.0%)
Discontinued	146 (41.1%)	201 (56.1%)	157 (44.2%)	504 (47.2%)
Patients with Treatment Reinitiation	73 (20.6%)	89 (24.9%)	99 (27.9%)	261 (24.4%)
Patients with Treatment Suspension but no Reinitiation	46 (13.0%)	23 (6.4%)	21 (5.9%)	90 (8.4%)
Patients without Treatment Suspension	27 (7.6%)	89 (24.9%)	37 (10.4%)	153 (14.3%)
Did Not Receive Study Drug	2 (0.6%)	4 (1.1%)	1 (0.3%)	7 (0.7%)
Primary Reason for Discontinuation of Study Drug				
Centrally Confirmed Radiographic Progression	26 (7.3%)	66 (18.4%)	37 (10.4%)	129 (12.1%)
PSA Progression Notification from Sponsor	2 (0.6%)	20 (5.6%)	5 (1.4%)	27 (2.5%)
Adverse Event	73 (20.6%)	36 (10.1%)	63 (17.7%)	172 (16.1%)
Development of Castration Resistance	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (0.2%)
Patient Decision to Discontinue Study Treatment	26 (7.3%)	32 (8.9%)	25 (7.0%)	83 (7.8%)
Protocol Deviation	2 (0.6%)	2 (0.6%)	1 (0.3%)	5 (0.5%)
Lost to Follow-Up	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (< 0.1%)
Study Terminated by Sponsor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Medication Error Without Associated Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other, Specify†	17 (4.8%)	41 (11.5%)	26 (7.3%)	84 (7.9%)
Long-Term Follow-up (LTFU) Phase Disposition				
Ongoing (still in LTFU)	67 (18.9%)	104 (29.1%)	62 (17.5%)	233 (21.8%)
Off Study	81 (22.8%)	101 (28.2%)	96 (27.0%)	278 (26.0%)
Primary Reason for Discontinuation of Long-Term Follow-up				
Death	33 (9.3%)	54 (15.1%)	42 (11.8%)	129 (12.1%)
Lost to Follow-up	3 (0.8%)	3 (0.8%)	4 (1.1%)	10 (0.9%)
Withdrew Consent to be Followed	40 (11.3%)	36 (10.1%)	38 (10.7%)	114 (10.7%)
Sponsor Decision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other, Specify†	5 (1.4%)	8 (2.2%)	12 (3.4%)	25 (2.3%)

The data cut-off date is 31 Jan 2023. Treatment phase is defined as the period of time from the date of the first dose of study drug up to the last dose date. Long-term follow-up (LTFU) phase is the period from study drug discontinuation to the death date or last known survival date. Ongoing patients are defined as patients still in the respective phases. Off study patients are defined as patients who are no longer being followed up for study for any reason (including for overall survival). † Other, specify: Thirty seven patients discontinued from study drug due to PI decision/disease progression by local conventional scans/PSA information (5 patients for ENZA+LA, 11 patients for ENZA and 21 for PBO+LA), ten patients due to PSMA-PET determination of progression (2 patients for ENZA+LA and 8

for PBO+LA), seven patients due to site closure (2 patients for ENZA+LA, 4 patients for ENZA and 1 for PBO+LA). Thirty patients discontinued due to other miscellaneous reasons as in listing 16.2.1.

Table 7. Patient Disposition by Study Treatment Status (Safety Population)

	ENZA + LA (N = 353)	**PBO + LA (N = 354)**	**ENZA (N = 354)**	**Total (N = 1061)**
Study Treatment Status				
Patients with Treatment Suspension	321 (90.9%)	240 (67.8%)	304 (85.9%)	865 (81.5%)
Patients with Treatment Reinitiation	241 (68.3%)	203 (57.3%)	270 (76.3%)	714 (67.3%)
Patients with Treatment Suspension and without Reinitiation	80 (22.7%)	37 (10.5%)	34 (9.6%)	151 (14.2%)
Patients without Treatment Suspension	32 (9.1%)	114 (32.2%)	50 (14.1%)	196 (18.5%)

The data cut-off date is 31 Jan 2023.

Table 8. Patient Randomization by Stratum (ITT Population)

	ENZA+LA (N = 355)		**PBO+LA (N = 358)**		**ENZA (N = 355)**	
Randomization Stratum	**IVRS/IWRS (N = 355)**	**CRF (N = 355)**	**IVRS/IWRS (N = 358)**	**CRF (N = 358)**	**IVRS/IWRS (N = 355)**	**CRF (N = 355)**
Screening PSA ≤ 10 ng/mL	275 (77.5%)	278 (78.3%)	276 (77.1%)	273 (76.3%)	274 (77.2%)	272 (76.6%)
Screening PSA > 10 ng/mL	80 (22.5%)	77 (21.7%)	82 (22.9%)	83 (23.2%)	81 (22.8%)	82 (23.1%)
PSADT ≤ 3 months	71 (20.0%)	69 (19.4%)	74 (20.7%)	80 (22.3%)	73 (20.6%)	76 (21.4%)
PSADT > 3 - ≤ 9 months	284 (80.0%)	285 (80.3%)	284 (79.3%)	277 (77.4%)	282 (79.4%)	278 (78.3%)
PSADT > 9 months	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)
Prior Hormonal Therapy - Yes	110 (31.0%)	107 (30.1%)	112 (31.3%)	113 (31.6%)	110 (31.0%)	112 (31.5%)
Prior Hormonal Therapy - No	245 (69.0%)	248 (69.9%)	246 (68.7%)	245 (68.4%)	245 (69.0%)	243 (68.5%)

The data cut-off date is 31 Jan 2023

IVRS/IWRS: stratification as recorded in Interactive Voice Response System/ Interactive Web Response System at time of randomizatio n. CRF: stratification as recorded in the electronic case report forms.

Conduct of the study

Protocol amendments

The original protocol (v 1.0) dated from 3 Sep 2014. Since them, 4 protocol amendments were issued on the following dates:

Original Protocol	V 1.0 – 03 Sep 2014

Amendment 1	V 2.0 – 09 Mar 2017
Amendment 2	V 3.0 – 20 Aug 2018
Amendment 3	V 4.0 – 31 Mar 2020
Amendment 4	V 5.0 – 29 Oct 2021

Amendment 4 (29 Oct 2021)

In this Amendment the study primary endpoint was repowered, and the interim analysis of the primary endpoint was removed. The rationale for repowering the study primary endpoint and removing the MFS interim analysis was based on recent clinical trial results of enzalutamide and other androgen targeting agents in similar comparator populations in which it became apparent that the statistical analysis plan for EMBARK was too conservative with a target hazard ratio of 0.65 for MFS. The PROSPER (HR = 0.29; 95% CI: 0.24, 0.35; P<0.001) and SPARTAN (HR = 0.28; 95% CI: 0.23, 0.35; P<0.001) studies demonstrated statistically significant and clinically meaningful improvement of MFS in patients with non-metastatic castration-resistant prostate cancer. Additionally, recently presented data from a subpopulation of the STAMPEDE study showed robust clinical benefits for abiraterone acetate plus prednisone with or without enzalutamide added to ADT (MFS HR= 0.53; 95% CI: 0.44, 0.64; P<0.0001) in patients similar to EMBARK with non-metastatic hormone sensitive prostate cancer. These results suggested a consistently strong treatment effect observed for Enzalutamide across the prostate cancer disease spectrum using MFS as primary endpoint. Therefore, the interim analysis of MFS was removed and the target hazard ratio for the primary MFS analysis was lowered from 0.65 to 0.58. Based on the lower target hazard ratio of 0.58, the final analysis was to be triggered by a lower number of events (197 instead of 336).

Protocol deviations.

Table 9. Major Protocol Deviations (ITT Population)

Categories	ENZA + LA (N=355)	PBO + LA (N=358)	ENZA (N=355)	Total (N=1068)
Number of Patients with At Least One Major Protocol Deviation	17 (4.8%)	11 (3.1%)	23 (6.5%)	51 (4.8%)
Major Deviation				
Administrative Criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant Medication Criteria	4 (1.1%)	3 (0.8%)	0 (0.0%)	7 (0.7%)
Efficacy Criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eligibility and Entry Criteria	3 (0.8%)	1 (0.3%)	5 (1.4%)	9 (0.8%)
IP Compliance	9 (2.5%)	6 (1.7%)	16 (4.5%)	31 (2.9%)
Informed Consent	0 (0.0%)	1 (0.3%)	1 (0.3%)	2 (0.2%)
Laboratory Assessment Criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious Adverse Event Criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Source Document Criteria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Procedures Criteria	0 (0.0%)	0 (0.0%)	2 (0.6%)	2 (0.2%)
Visit Schedule Criteria	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (<0.1%)
Other Criteria	1 (0.3%)	0 (0.0%)	1 (0.3%)	2 (0.2%)

The data cut-off date is 31JAN2023.

Baseline data

Demographics and baseline disease characteristics

Table 10. Patient Demographic and Baseline Characteristics (ITT Population)

Baseline Characteristic	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
Age Category (years)				
< 65	81 (22.8%)	91 (25.4%)	91 (25.6%)	263 (24.6%)
65 to < 75	201 (56.6%)	180 (50.3%)	174 (49.0%)	555 (52.0%)
≥ 75	73 (20.6%)	87 (24.3%)	90 (25.4%)	250 (23.4%)
Age				
n	355	358	355	1068
Mean (SD)	69.1 (6.49)	69.1 (7.30)	69.1 (7.65)	69.1 (7.16)
Median	69.0	70.0	69.0	69.0
Min, Max	51.0, 87.0	50.0, 92.0	49.0, 93.0	49.0, 93.0
Race				
American Indian or Alaskan Native	4 (1.1%)	1 (0.3%)	0 (0.0%)	5 (0.5%)
Asian	26 (7.3%)	26 (7.3%)	26 (7.3%)	78 (7.3%)
Black or African American	16 (4.5%)	16 (4.5%)	15 (4.2%)	47 (4.4%)
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (< 0.1%)
White	293 (82.5%)	301 (84.1%)	295 (83.1%)	889 (83.2%)
Multiple	2 (0.6%)	4 (1.1%)	4 (1.1%)	10 (0.9%)
Other	3 (0.8%)	5 (1.4%)	1 (0.3%)	9 (0.8%)
Not Reported	10 (2.8%)	5 (1.4%)	14 (3.9%)	29 (2.7%)
Ethnicity				
Hispanic or Latino	17 (4.8%)	24 (6.7%)	18 (5.1%)	59 (5.5%)
Not Hispanic or Latino	319 (89.9%)	322 (89.9%)	320 (90.1%)	961 (90.0%)
Not Reported/Unknown	19 (5.4%)	12 (3.4%)	17 (4.8%)	48 (4.5%)
Geographic Region				
North America	144 (40.6%)	137 (38.3%)	133 (37.5%)	414 (38.8%)
Europe	130 (36.6%)	128 (35.8%)	146 (41.1%)	404 (37.8%)
Rest of World	81 (22.8%)	93 (26.0%)	76 (21.4%)	250 (23.4%)
Weight (kg)				
n	355	357	355	1067
Mean (SD)	87.5 (15.16)	87.2 (15.86)	87.5 (15.55)	87.4 (15.51)
Median	85.0	85.7	85.0	85.4
Min, Max	55.6, 157.7	53.7, 148.2	50.0, 171.8	50.0, 171.8
Missing	0	1	0	1
Height (cm)				
n	353	354	354	1061
Mean (SD)	174.9 (8.20)	175.2 (7.84)	174.8 (7.66)	175.0 (7.90)
Median	175.0	175.3	175.0	175.0
Min, Max	144.8, 196.0	150.6, 198.1	152.4, 198.1	144.8, 198.1
Missing	2	4	1	7
Body Mass Index (kg/m^2)				
n	353	354	354	1061
Mean (SD)	28.5 (4.22)	28.3 (4.37)	28.6 (4.70)	28.5 (4.43)

Baseline Characteristic	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
Median	28.1	28.0	27.9	28.0
Min, Max	19.9, 47.1	18.5, 45.9	17.3, 53.2	17.3, 53.2
Missing	2	4	1	7
Baseline ECOG Performance Status				
0	328 (92.4%)	336 (93.9%)	321 (90.4%)	985 (92.2%)
1	26 (7.3%)	21 (5.9%)	34 (9.6%)	81 (7.6%)
2	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (< 0.1%)
Missing	0	1 (0.3%)	0	1 (< 0.1%)
Serum PSA (ng/mL)				
n	355	356	354	1065
Mean (SD)	8.1 (17.56)	8.5 (11.76)	7.5 (6.54)	8.0 (12.77)
Median	5.0	5.5	5.3	5.2
Min, Max	1.0, 308.3	1.1, 163.3	1.1, 37.0	1.0, 308.3
Missing	0	2	1	3
Screening PSADT Category (DT)†				
≤ 3 Months	69 (19.4%)	80 (22.3%)	76 (21.4%)	225 (21.1%)
> 3 - ≤ 6 Months	187 (52.7%)	142 (39.7%)	164 (46.2%)	493 (46.2%)
> 6 - ≤ 9 Months	98 (27.6%)	135 (37.7%)	114 (32.1%)	347 (32.5%)
> 9 Months	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.3%)
PSADT (months)				
n	355	358	355	1068
Mean (SD)	4.9 (2.04)	5.2 (2.20)	5.1 (2.15)	5.0 (2.13)
Median	4.6	5.0	5.0	4.9
Min, Max	0.9, 9.6	1.1, 10.8	1.0, 18.9	0.9, 18.9
History of Cardiovascular Disease				
Yes	42 (11.8%)	42 (11.7%)	47 (13.2%)	131 (12.3%)
No	313 (88.2%)	316 (88.3%)	308 (86.8%)	937 (87.7%)
Prior Hormonal Therapy				
Yes	107 (30.1%)	113 (31.6%)	112 (31.5%)	332 (31.1%)
No	248 (69.9%)	245 (68.4%)	243 (68.5%)	736 (68.9%)
Prior Prostatectomy				
Yes	269 (75.8%)	254 (70.9%)	265 (74.6%)	788 (73.8%)
No	86 (24.2%)	104 (29.1%)	90 (25.4%)	280 (26.2%)
Prior Radiation Therapy				
Yes	265 (74.6%)	283 (79.1%)	256 (72.1%)	804 (75.3%)
No	90 (25.4%)	75 (20.9%)	99 (27.9%)	264 (24.7%)
Prior Prostatectomy and Radiation Therapy				
Yes	179 (50.4%)	179 (50.0%)	166 (46.8%)	524 (49.1%)
No	176 (49.6%)	179 (50.0%)	189 (53.2%)	544 (50.9%)
Patients with Pelvic Soft Tissue Lesion at Baseline (CRF)				
n	16 (4.5%)	7 (2.0%)	9 (2.5%)	32 (3.0%)

The data cut-off date is 31 Jan 2023. † PSADT categories are summarized based on data collected in study CRF pages.

Medical history, prior and subsequent therapies.

Table 11: Medical History for Prostate Cancer and Disease Characteristics (ITT Population)

Baseline Characteristic	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
Time (Months) from Initial Diagnosis to Randomization				
n	355	358	355	1068
Mean (SD)	67.2 (44.25)	70.1 (49.00)	72.7 (52.03)	70.0 (48.54)
Median	56.9	63.7	61.7	60.9
Min, Max	5.8, 222.4	5.7, 305.5	6.0, 297.4	5.7, 305.5
Primary Gleason Score				
n	327	335	319	981
Mean (SD)	3.6 (0.57)	3.6 (0.61)	3.6 (0.58)	3.6 (0.59)
Median	4.0	4.0	4.0	4.0
Min, Max	2.0, 5.0	2.0, 5.0	2.0, 5.0	2.0, 5.0
Missing	28	23	36	87
Primary Gleason Score Group				
< 4	129 (36.3%)	141 (39.4%)	145 (40.8%)	415 (38.9%)
≥ 4	198 (55.8%)	194 (54.2%)	174 (49.0%)	566 (53.0%)
Unknown	1 (0.3%)	1 (0.3%)	5 (1.4%)	7 (0.7%)
Missing	27 (7.6%)	22 (6.1%)	31 (8.7%)	80 (7.5%)
Secondary Gleason Score				
n	327	335	319	981
Mean (SD)	3.7 (0.70)	3.7 (0.73)	3.7 (0.75)	3.7 (0.73)
Median	4.0	4.0	4.0	4.0
Min, Max	2.0, 5.0	2.0, 5.0	2.0, 5.0	2.0, 5.0
Missing	28	23	36	87
Total Gleason Score				
n	354	357	350	1061
Mean (SD)	7.4 (0.96)	7.3 (1.01)	7.2 (1.03)	7.3 (1.00)
Median	7.0	7.0	7.0	7.0
Min, Max	4.0, 10.0	5.0, 10.0	4.0, 10.0	4.0, 10.0
Missing	1	1	5	7
Total Gleason Score Group				
Low (2-4)	1 (0.3%)	0 (0.0%)	3 (0.8%)	4 (0.4%)
Medium (5-7)	233 (65.6%)	244 (68.2%)	236 (66.5%)	713 (66.8%)
High (8-10)	120 (33.8%)	113 (31.6%)	111 (31.3%)	344 (32.2%)
Unknown	1 (0.3%)	1 (0.3%)	5 (1.4%)	7 (0.7%)
Clinical Stage				
TX	34 (9.6%)	24 (6.7%)	32 (9.0%)	90 (8.4%)
T0	3 (0.8%)	1 (0.3%)	2 (0.6%)	6 (0.6%)

Baseline Characteristic	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
T1	70 (19.7%)	76 (21.2%)	82 (23.1%)	228 (21.3%)
T2	134 (37.7%)	146 (40.8%)	146 (41.1%)	426 (39.9%)
T3	109 (30.7%)	109 (30.4%)	91 (25.6%)	309 (28.9%)
T4	5 (1.4%)	2 (0.6%)	2 (0.6%)	9 (0.8%)
Pathologic Tumor Stage				
pTX (not assessed)	15 (4.2%)	15 (4.2%)	9 (2.5%)	39 (3.7%)
pT1 (pT1a, pT1b, pT1c)	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (0.2%)
pT2 (pT2a, pT2b, pT2c)	77 (21.7%)	85 (23.7%)	81 (22.8%)	243 (22.8%)
pT3x (a/b Status Unknown)	10 (2.8%)	9 (2.5%)	5 (1.4%)	24 (2.2%)
pT3a	80 (22.5%)	69 (19.3%)	91 (25.6%)	240 (22.5%)
pT3b	84 (23.7%)	73 (20.4%)	78 (22.0%)	235 (22.0%)
pT4	3 (0.8%)	1 (0.3%)	1 (0.3%)	5 (0.5%)
Lymph Nodes Stage				
pNX (not assessed)	68 (19.2%)	65 (18.2%)	65 (18.3%)	198 (18.5%)
pN0	171 (48.2%)	156 (43.6%)	165 (46.5%)	492 (46.1%)
pN1	30 (8.5%)	33 (9.2%)	35 (9.9%)	98 (9.2%)

The data cut-off date is 31 Jan 2023.

Prior anticancer therapy

Prior therapy for prostate cancer was generally similar across the 3 treatment groups.

- 32.2% patients had at least 1 unique prior prostate cancer therapy (31.3% in the enzalutamide plus leuprolide group, 32.7% in the placebo plus leuprolide group, and 32.7% in the enzalutamide monotherapy group).
- 16.2% patients had at least 1 unique prior hormonal therapy (14.1% in the enzalutamide plus leuprolide group, 16.5% in the placebo plus leuprolide group, and 18.0% in the enzalutamide monotherapy group).
- 23.0% patients had prior non-hormonal therapies (22.3% in the enzalutamide plus leuprolide group, 23.5% in the placebo plus leuprolide group, and 23.4% in the enzalutamide monotherapy group).
- 0.4% patients used prior bisphosphonate or denosumab for non-prostate cancer therapy at baseline (0.6% in the enzalutamide plus leuprolide group, 0% in the placebo plus leuprolide group, and 0.6% in the enzalutamide monotherapy group).
- The majority of patients had received no prior hormonal therapy (69.9% in the enzalutamide plus leuprolide group, 68.4% in the placebo plus leuprolide group, and 68.5% in the enzalutamide monotherapy group).

The most frequent (> 5% patients in any treatment group) prior drug therapies for prostate cancer were leuprorelin (17.7% in the enzalutamide plus leuprolide group vs 19.8% in the placebo plus leuprolide group, and 18.6% in the enzalutamide monotherapy group), bicalutamide (9.0% vs 10.9% vs 10.7%), and goserelin (7.3% vs 5.6% vs 6.2%).

Subsequent anticancer therapy

Table 12. Subsequent Antineoplastic Therapy Initiated After Treatment Discontinuation Reported for at Least 1% of Patients in Any Treatment Group (ITT Population)

ATC Level Description† Generic Name	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)	Total (N = 1068)
Number of Patients Taking at Least One Subsequent Antineoplastic Therapy	58 (16.3%)	139 (38.8%)	84 (23.7%)	281 (26.3%)
Antineoplastic Agents	9 (2.5%)	38 (10.6%)	18 (5.1%)	65 (6.1%)
Docetaxel	6 (1.7%)	31 (8.7%)	15 (4.2%)	52 (4.9%)
Cabazitaxel	2 (0.6%)	14 (3.9%)	7 (2.0%)	23 (2.2%)
Cyclophosphamide	0 (0.0%)	4 (1.1%)	1 (0.3%)	5 (0.5%)
Corticosteroids	6 (1.7%)	10 (2.8%)	3 (0.8%)	19 (1.8%)
Prednisone‡	6 (1.7%)	10 (2.8%)	3 (0.8%)	19 (1.8%)
Drugs For Treatment Of Bone Diseases	5 (1.4%)	3 (0.8%)	5 (1.4%)	13 (1.2%)
Denosumab	3 (0.8%)	3 (0.8%)	4 (1.1%)	10 (0.9%)
Endocrine Therapy	56 (15.8%)	132 (36.9%)	76 (21.4%)	264 (24.7%)
Leuprorelin	40 (11.3%)	79 (22.1%)	44 (12.4%)	163 (15.3%)
Enzalutamide	9 (2.5%)	44 (12.3%)	11 (3.1%)	64 (6.0%)
Abiraterone	11 (3.1%)	37 (10.3%)	15 (4.2%)	63 (5.9%)
Bicalutamide	9 (2.5%)	18 (5.0%)	20 (5.6%)	47 (4.4%)
Triptorelin	6 (1.7%)	9 (2.5%)	13 (3.7%)	28 (2.6%)
Goserelin	4 (1.1%)	9 (2.5%)	9 (2.5%)	22 (2.1%)
Darolutamide	3 (0.8%)	15 (4.2%)	3 (0.8%)	21 (2.0%)
Degarelix	3 (0.8%)	6 (1.7%)	12 (3.4%)	21 (2.0%)
Apalutamide	1 (0.3%)	6 (1.7%)	4 (1.1%)	11 (1.0%)
Immunostimulants	5 (1.4%)	11 (3.1%)	5 (1.4%)	21 (2.0%)
Sipuleucel-T	5 (1.4%)	11 (3.1%)	5 (1.4%)	21 (2.0%)
Therapeutic Radiopharmaceuticals	1 (0.3%)	6 (1.7%)	3 (0.8%)	10 (0.9%)
Radium Ra 223 Dichloride	0 (0.0%)	6 (1.7%)	1 (0.3%)	7 (0.7%)
Uncoded	0 (0.0%)	8 (2.2%)	1 (0.3%)	9 (0.8%)
Blinded Therapy	0 (0.0%)	5 (1.4%)	0 (0.0%)	5 (0.5%)

The data cut-off date is 31 Jan 2023.

All Subsequent Antineoplastic therapies used to treat prostate cancer which occurred in the study are included. Therapeutic class is based on WHODRUG version 2022-03. At each level of summarization (overall, drug class, and generic name), patients are counted only once.† ATC Level 2 description is used. If unavailable, ATC Level 1 description is used.‡
Systemic prednisone was reported for some patients with other antineoplastic therapy as a combination regimen.

Numbers analysed

Populations analysed

The number of participants included in each analysis population is provided in Table 12.

Table 13. Patient populations

Patient Population	ENZA + LA (N=355)	PBO + LA (N=358)	ENZA (N=355)	Total (N=1068)
ITT Population	355 (100.0%)	358 (100.0%)	355 (100.0%)	1068 (100.0%)
Evaluable ITT Population	354 (99.7%)	356 (99.4%)	354 (99.7%)	1064 (99.6%)
Safety Population	353 (99.4%)	354 (98.9%)	354 (99.7%)	1061 (99.3%)

The data cut-off date is 31JAN2023.

Outcomes and estimation

The efficacy analyses were performed using the data up to the primary completion date (PCD) cut-off date of 31 January 2023. The analysis of the key secondary endpoint OS was a prespecified interim analysis. Analyses of all other secondary efficacy endpoints were final analyses.

Primary efficacy endpoint

BICR assessed MFS (Enzalutamide Plus Leuprolide vs Placebo Plus Leuprolide)

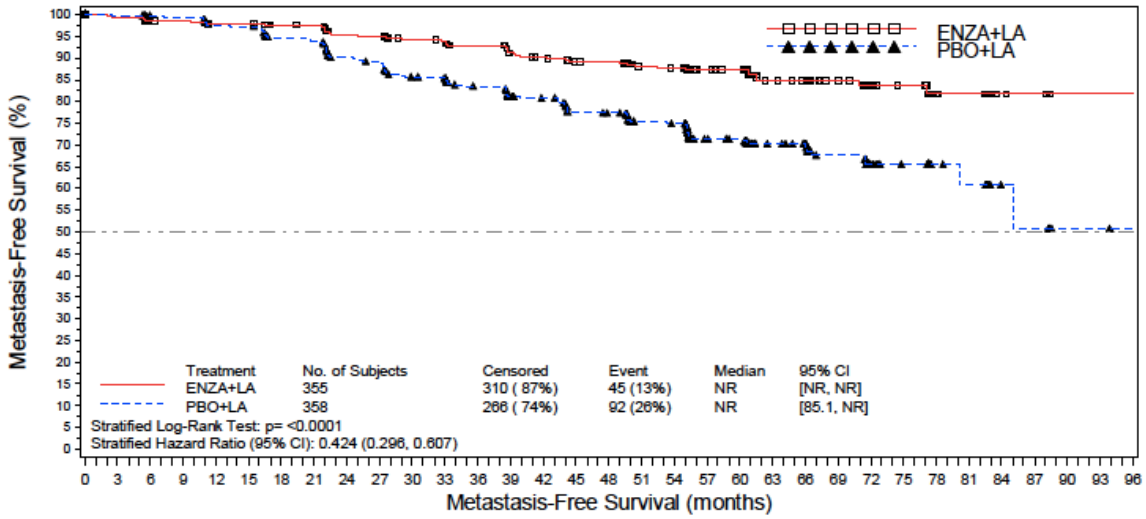
Table 14. MFS Based on BICR Assessment for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Primary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**
Status of MFS Follow-up		
Events†	45 (12.7%)	92 (25.7%)
Progression by Independent Central Review	37 (10.4%)	84 (23.5%)
Bone Progression	12 (3.4%)	24 (6.7%)
Soft Tissue Progression	23 (6.5%)	54 (15.1%)
Concurrent Bone and Soft Tissue Progression	2 (0.6%)	6 (1.7%)
Death Without Documented Radiographic Progression	8 (2.3%)	8 (2.2%)
Status of MFS Follow-up		
Censored‡	310 (87.3%)	266 (74.3%)
No Postbaseline Assessments	11 (3.1%)	7 (2.0%)
Metastatic Disease at Randomization	1 (0.3%)	2 (0.6%)
Initiation of Antineoplastic Therapy	36 (10.1%)	67 (18.7%)
Abiraterone Acetate	0 (0.0%)	3 (0.8%)
Cytotoxic Chemotherapy	9 (2.5%)	4 (1.1%)
Cytotoxic Chemotherapy + Other	0 (0.0%)	1 (0.3%)
First Prostate Cancer Antineoplastic Therapy Date	0 (0.0%)	1 (0.3%)
Hormonal Therapy	25 (7.0%)	56 (15.6%)
Hormonal Therapy + Prostate Cancer Vaccine	0 (0.0%)	1 (0.3%)
Other	1 (0.3%)	1 (0.3%)
Prostate Cancer Vaccine	1 (0.3%)	0 (0.0%)
2+ Missed Visits	4 (1.1%)	5 (1.4%)
No Metastatic Disease or Death	258 (72.7%)	185 (51.7%)
MFS Based on K-M Estimates (in Months)		
n	355	358
25th Percentile	NR	53.3

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
75th Percentile	NR	NR
P-value§	< 0.0001	
Hazard Ratio (95% CI)§	0.424 (0.296, 0.607)	
Probability of Being Event Free Based on K-M Estimates at:		
Year 1 (95% CI)	0.979 (0.957, 0.990)	0.976 (0.953, 0.988)
Year 2 (95% CI)	0.951 (0.922, 0.970)	0.901 (0.863, 0.929)
Year 3 (95% CI)	0.929 (0.895, 0.952)	0.835 (0.789, 0.872)
Observed Follow-up Time for Censored Patients¶ (in Months)		
n	310	266
25th Percentile	49.8	33.9
Median	60.7	56.3
75th Percentile	71.4	66.3
Min, Max	0.03, 88.41	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)		
n	355	358
25th Percentile	54.8	44.1
Median (95% CI)	60.7 (60.6, 60.8)	60.6 (55.8, 60.7)
75th Percentile	71.7	71.6

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Based on the earliest contributing event (radiographic progression or death).‡ Patients who were not known to have had an MFS event at the time of analysis data cutoff, started new antineoplastic therapy, systemic radiopharmaceuticals, or any other anti-cancer therapy are censored at date of last assessment showing no objective evidence of radiographic progression.
Patients randomized but later confirmed to have metastatic disease are censored on date of randomization.§ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined
above and is relative to PBO+LA with < 1 favoring ENZA+LA.¶ Calculated as (date of last assessment showing no evidence of radiograp hic progression - randomization date + 1) / 30.4375.

Figure 5. K-M Curves for MFS by BICR for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups – Primary Efficacy Analysis (ITT Population)



ENZA+LA:
Event/Cum. Events 0/0 2/2 3/5 0/5 2/7 0/7 1/8 0/8 8/16 1/17 2/19 1/20 3/23 5/28 3/31 3/34 0/34 3/37 1/38 1/39 0/39 4/43 0/43 0/43 1/44 0/44 1/45 0/45 0/45 0/45 0/45 0/45 0/45
Patients at Risk 355 339 331 330 324 324 318 317 304 303 292 290 281 270 265 252 251 236 234 183 180 119 116 83 60 51 24 22 6 5 0 0 0
PBO+LA:
Event/Cum. Events 0/0 1/1 0/1 1/2 6/8 1/9 9/18 2/20 12/32 3/35 11/46 1/47 5/52 7/59 1/60 9/69 0/69 5/74 1/75 8/83 0/83 2/85 0/85 3/88 2/90 0/90 0/90 1/91 0/91 1/92 0/92 0/92 0/92
Patients at Risk 358 344 335 334 321 320 303 301 280 276 259 256 238 226 221 205 203 185 183 141 138 93 88 66 32 27 15 13 6 5 1 1 0

The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/ti/f_14_02_01_01_01_mfslcr.sas 12APR23:18:04 Output File: f_14_02_01_01_01_mfslcr.rtf

Key secondary endpoints

MFS (Enzalutamide Monotherapy vs Placebo Plus Leuprolide)

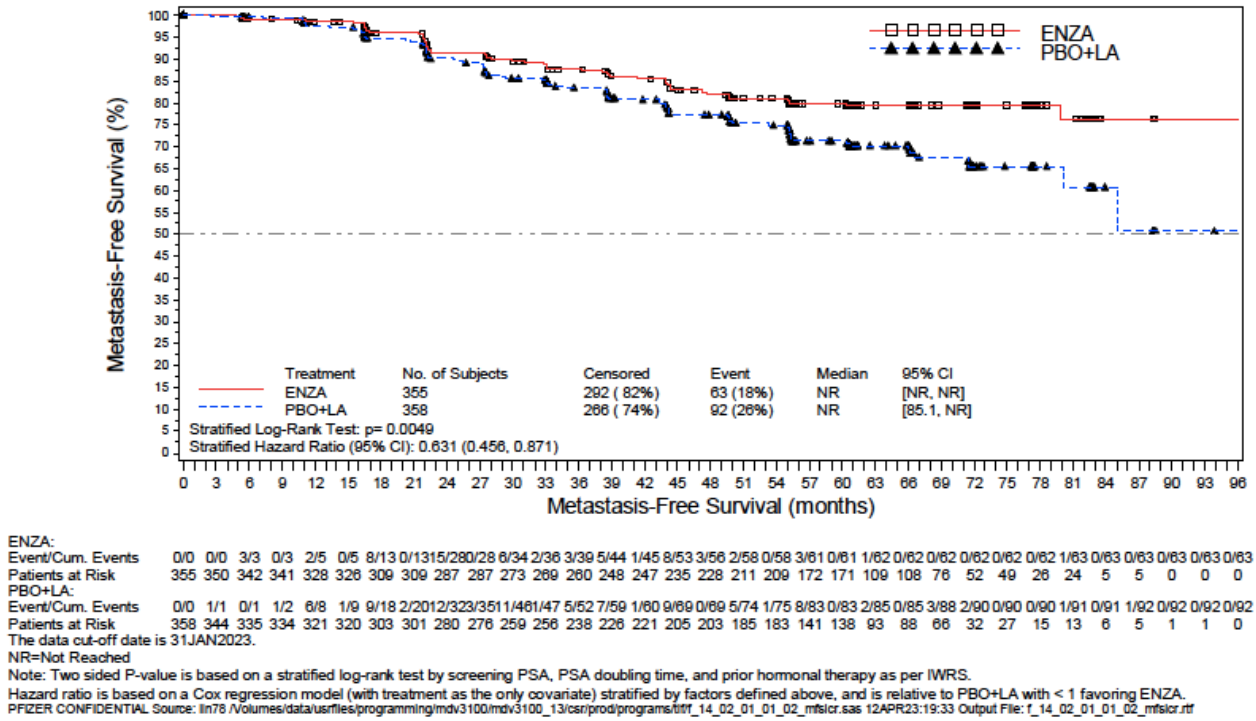
Table 15: MFS Based on BICR Assessment for Enzalutamide vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)

	ENZA (N = 355)	**PBO + LA (N = 358)**
Status of MFS Follow-up		
Events†	63 (17.7%)	92 (25.7%)
Progression by Independent Central Review	54 (15.2%)	84 (23.5%)
Bone Progression	24 (6.8%)	24 (6.7%)
Soft Tissue Progression	29 (8.2%)	54 (15.1%)
Concurrent Bone and Soft Tissue Progression	1 (0.3%)	6 (1.7%)
Death Without Documented Radiographic Progression	9 (2.5%)	8 (2.2%)
Status of MFS Follow-up		
Censored‡	292 (82.3%)	266 (74.3%)
No Postbaseline Assessments	4 (1.1%)	7 (2.0%)
Metastatic Disease at Randomization	1 (0.3%)	2 (0.6%)
Initiation of Antineoplastic Therapy	44 (12.4%)	67 (18.7%)
Abiraterone Acetate	0 (0.0%)	3 (0.8%)
Bone Targeting Agent + Hormonal Therapy	2 (0.6%)	0 (0.0%)
Cytotoxic Chemotherapy	3 (0.8%)	4 (1.1%)
Cytotoxic Chemotherapy + Other	0 (0.0%)	1 (0.3%)
First Prostate Cancer Antineoplastic Therapy Date	0 (0.0%)	1 (0.3%)
Hormonal Therapy	38 (10.7%)	56 (15.6%)
Hormonal Therapy + Prostate Cancer Vaccine	0 (0.0%)	1 (0.3%)
Other	1 (0.3%)	1 (0.3%)

	ENZA (N = 355)	**PBO + LA (N = 358)**
2+ Missed Visits	4 (1.1%)	5 (1.4%)
No Metastatic Disease or Death	239 (67.3%)	185 (51.7%)
MFS Based on K-M Estimates (in Months)		
n	355	358
25th Percentile	NR	53.3
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
75th Percentile	NR	NR
P-value§	0.0049	
Hazard Ratio (95% CI)§	0.631 (0.456, 0.871)	
Probability of Being Event Free Based on K-M Estimates at:		
Year 1 (95% CI)	0.986 (0.966, 0.994)	0.976 (0.953, 0.988)
Year 2 (95% CI)	0.914 (0.878, 0.940)	0.901 (0.863, 0.929)
Year 3 (95% CI)	0.878 (0.837, 0.909)	0.835 (0.789, 0.872)
Observed Follow-up Time for Censored Patients¶ (in Months)		
n	292	266
25th Percentile	49.5	33.9
Median	60.7	56.3
75th Percentile	71.5	66.3
Min, Max	0.03, 88.48	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)		
n	355	358
25th Percentile	49.9	44.1
Median (95% CI)	60.7 (60.6, 60.8)	60.6 (55.8, 60.7)
75th Percentile	71.7	71.6

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Based on the earliest contributing event (radiographic progression or death).‡ Patients who were not known to have had an MFS event at the time of analysis data cutoff, started new antineoplastic therapy, systemic radiopharmaceuticals, or any other anti-cancer therapy are censored at date of last assessment showing no objective evidence of radiographic progression.
Patients randomized but later confirmed to have metastatic disease are censored on date of randomization§ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA
¶ Calculated as (date of last assessment showing no evidence of radiographic progression - randomization date + 1) / 30.4375.

Figure 6: K-M Curves for MFS by BICR for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Key Secondary Efficacy Analysis (ITT Population)



Time to PSA progression

Table 16. Time to PSA Progression - Key Secondary Efficacy Analysis (ITT Population)

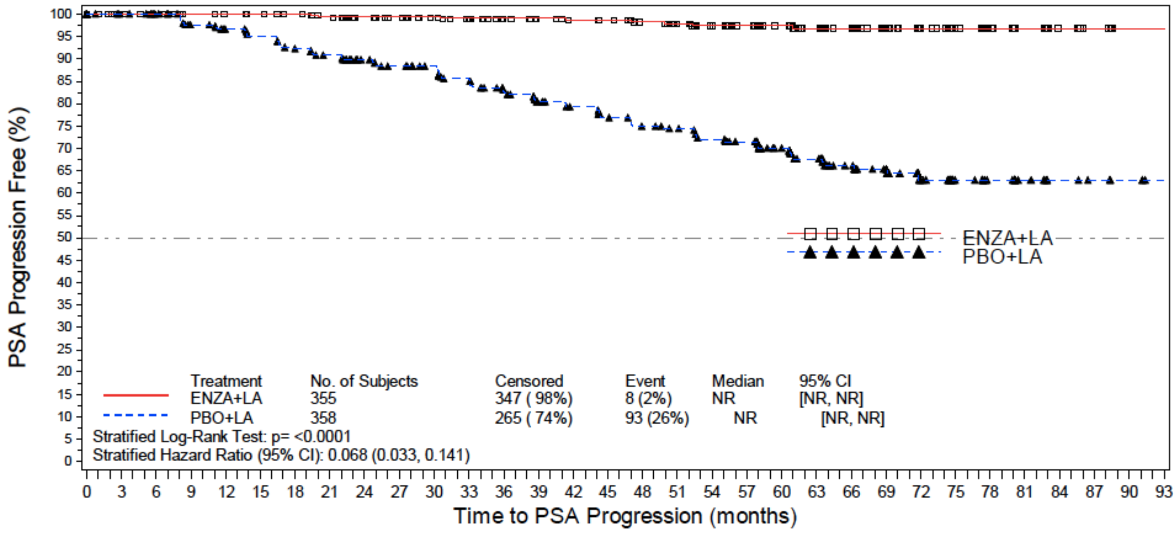
	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of Prostate-Specific Antigen Follow-up			
Prostate-Specific Antigen Progression†	8 (2.3%)	93 (26.0%)	37 (10.4%)
Censored‡	347 (97.7%)	265 (74.0%)	318 (89.6%)
Time to Prostate-Specific Antigen Progression Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	NR	47.1	NR
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
P-value§	< 0.0001		< 0.0001
Hazard Ratio (95% CI)§	0.068 (0.033, 0.141)		0.331 (0.226, 0.486)
Probability of Being Event Free Based on K-M Estimates at:			

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Year 1 (95% CI)	1.000 (1.000, 1.000)	0.967 (0.941, 0.982)	0.997 (0.979, 1.000)
Year 2 (95% CI)	0.994 (0.975, 0.998)	0.898 (0.859, 0.926)	0.978 (0.954, 0.989)
Year 3 (95% CI)	0.990 (0.970, 0.997)	0.827 (0.780, 0.866)	0.944 (0.911, 0.965)
Observed Follow-up Time for Censored Patients¶ (in Months)			
n	347	265	318
25th Percentile	38.8	28.7	38.7
Median	60.6	58.0	60.6
75th Percentile	70.1	69.0	69.1
Min, Max	0.03, 88.48	0.03, 91.37	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	41.0	36.3	42.3
Median (95% CI)	60.7 (58.0, 60.9)	60.6 (58.0, 61.0)	60.7 (58.0, 60.9)
75th Percentile	71.7	69.3	71.2

The data cut-off date is 31 Jan 2023. NR = Not Reached.
† Based on the PSA Progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria. ‡ Include patients who did not have confirmed PSA progression at the time of analysis data cutoff, or with anti-prostate cancer therapy, or with PSA progression after 2 or more consecutive missed PSA assessments, or without baseline and post-baseline PSA results, with time to PSA progression are censored at date of last assessment indicating no evidence of confirmed PSA progression, last assessment date prior to therapy, the date of last PSA assessment prior to the missed assessments, or the date of randomization respectively. § Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.

¶ Calculated as (date of last assessment showing no evidence of PSA progression - randomization date + 1) / 30.4375.

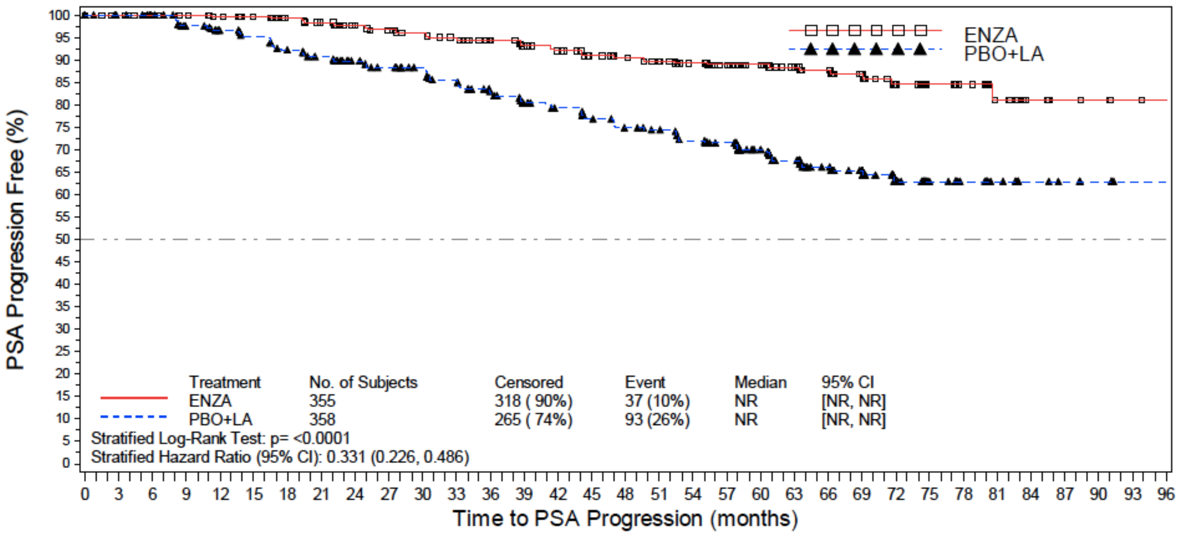
Figure 7.K-M Curves for Time to PSA Progression for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)



ENZA+LA:																															
Event/Cum. Events	0/0	0/0	0/0	0/0	0/0	0/0	0/0	2/2	0/2	0/2	0/2	1/3	0/3	0/3	1/4	0/4	1/5	1/6	1/7	0/7	0/7	1/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
Patients at Risk	355	344	337	329	326	323	319	312	302	296	286	280	270	265	260	255	247	240	230	201	175	144	119	94	75	53	37	25	12	5	0	0
PBO+LA:																																
Event/Cum. Events	0/0	0/0	0/0	8/8	3/11	5/16	9/25	5/30	3/33	4/37	0/37	8/45	8/53	6/59	3/62	6/68	5/73	1/74	6/80	1/81	3/84	4/88	2/90	1/91	2/93	0/93	0/93	0/93	0/93	0/93	0/93	0/93
Patients at Risk	358	347	341	324	314	305	293	283	268	260	253	240	223	209	201	190	182	178	168	154	128	105	83	66	42	28	20	13	7	5	3	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_01_01_psaprog.sas 12APR23:19:35 Output File: f_14_02_02_01_01_psaprog.rtf

Figure 8. K-M Curves for Time to PSA Progression for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Key Secondary Efficacy Analysis (ITT Population)



ENZA:																																
Event/Cum. Events	0/0	0/0	0/0	0/0	1/1	0/1	1/2	3/5	2/7	3/10	2/12	3/15	2/17	3/20	3/23	3/26	1/27	2/29	1/30	1/31	0/31	1/32	1/33	1/34	2/36	0/36	0/36	1/37	0/37	0/37	0/37	0/37	0/37
Patients at Risk	355	352	346	337	328	322	311	303	291	285	279	273	262	252	246	234	228	222	213	188	168	133	108	86	63	45	37	21	8	4	3	1	0
PBO+LA:																																	
Event/Cum. Events	0/0	0/0	0/0	8/8	3/11	5/16	9/25	5/30	3/33	4/37	0/37	8/45	8/53	6/59	3/62	6/68	5/73	1/74	6/80	1/81	3/84	4/88	2/90	1/91	2/93	0/93	0/93	0/93	0/93	0/93	0/93	0/93	0/93
Patients at Risk	358	347	341	324	314	305	293	283	268	260	253	240	223	209	201	190	182	178	168	154	128	105	83	66	42	28	20	13	7	5	3	0	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_01_02_psaprog.sas 12APR23:19:35 Output File: f_14_02_02_01_02_psaprog.rtf

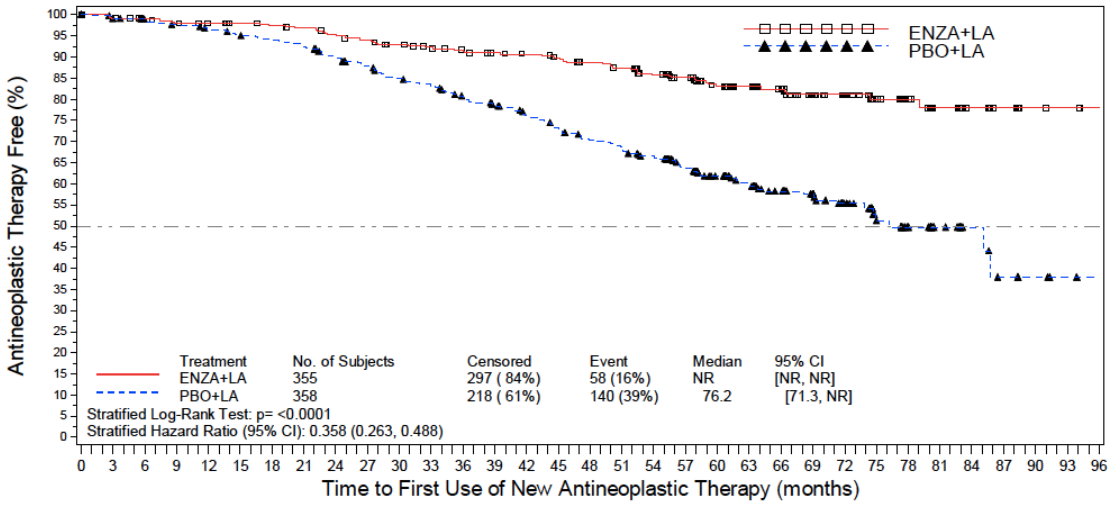
Time to Start of New Antineoplastic Therapy

Table 17. Time to First Use of New Antineoplastic Therapy - Key Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)
Status of Antineoplastic Therapy Follow-up			
Event†	58 (16.3%)	140 (39.1%)	84 (23.7%)
Censored	297 (83.7%)	218 (60.9%)	271 (76.3%)
Time to First Use of Antineoplastic Therapy Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	NR	43.7	64.4
Median (95% CI)	NR (NR, NR)	76.2 (71.3, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
P-value‡	< 0.0001		< 0.0001
Hazard Ratio (95% CI)‡	0.358 (0.263, 0.488)		0.540 (0.411, 0.709)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.980 (0.958, 0.990)	0.966 (0.940, 0.980)	0.986 (0.966, 0.994)
Year 2 (95% CI)	0.953 (0.924, 0.971)	0.898 (0.861, 0.926)	0.916 (0.881, 0.941)
Year 3 (95% CI)	0.916 (0.881, 0.942)	0.807 (0.761, 0.846)	0.844 (0.801, 0.879)
Observed Follow-up Time for Censored Patients§ (in Months)			
n	297	218	271
25th Percentile	55.4	55.2	57.9
Median	63.5	63.3	63.5
75th Percentile	74.5	71.8	74.4
Min, Max	0.03, 94.13	0.03, 93.90	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	55.7	58.0	58.0
Median (95% CI)	63.6 (61.5, 66.3)	63.7 (63.4, 66.3)	63.5 (63.0, 66.3)
75th Percentile	74.5	74.4	74.5

The data cut-off date is 31 Jan 2023. NR = Not Reached. † Based on the first postbaseline use of antineoplastic therapy for prostate cancer. ‡ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA. § Calculated as (date of last assessment prior to analysis data cutoff date - randomization date + 1) / 30.4375.

Figure 9. K-M Curves for Time to First Use of New Antineoplastic Therapy for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups – Key Secondary Efficacy Analysis (ITT Population)



ENZA+LA:
Event/Cum. Events 0/0 3/3 1/4 3/7 0/7 0/7 2/9 2/11 5/16 4/20 4/24 2/26 2/28 2/30 1/31 3/34 3/37 4/41 5/46 2/48 5/53 0/53 1/54 2/56 0/56 1/57 0/57 1/58 0/58 0/58 0/58 0/58 0/58
Patients at Risk 355 347 342 338 335 331 328 324 318 313 302 297 292 287 284 279 273 268 255 225 195 163 135 102 87 60 43 28 16 8 3 2 0
PBO+LA:
Event/Cum. Events 0/0 3/3 2/5 3/8 4/12 5/17 3/20 6/26 9/35 7/42 9/51 6/57 8/65 8/73 7/80 10/90 8/98 5/103 7/110 8/118 5/123 4/127 3/130 1/131 3/134 8/137 1/138 0/138 0/138 2/140 0/140 0/140 0/140
Patients at Risk 358 348 342 338 332 326 322 316 304 292 281 274 262 251 240 229 218 213 202 178 149 123 100 82 56 33 25 16 9 5 3 1 0
The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
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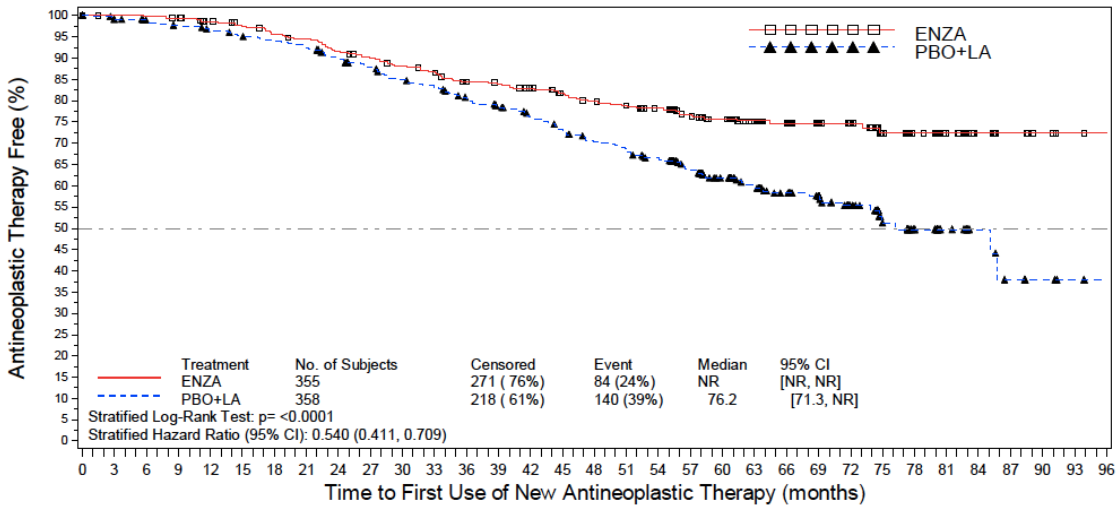
Figure 10. K-M Curves for Time to First Use of New Antineoplastic Therapy for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Key Secondary Efficacy Analysis



ENZA:
Event/Cum. Events 0/0 0/0 1/1 1/2 3/5 3/8 7/15 4/19 10/29 5/34 7/41 4/45 8/53 2/55 3/58 4/62 6/68 3/71 2/73 4/77 3/80 1/81 1/82 0/82 0/82 2/84 0/84 0/84 0/84 0/84 0/84 0/84 0/84
Patients at Risk 355 353 352 350 341 335 327 322 312 305 297 292 279 274 268 259 252 247 240 213 192 150 124 99 80 52 40 26 12 6 3 1 0
PBO+LA:
Event/Cum. Events 0/0 3/3 2/5 3/8 4/12 5/17 3/20 6/26 9/35 7/42 9/51 6/57 8/65 8/73 7/80 10/90 8/98 5/103 7/110 8/118 5/123 4/127 3/130 1/131 3/134 8/137 1/138 0/138 0/138 2/140 0/140 0/140 0/140
Patients at Risk 358 348 342 338 332 326 322 316 304 292 281 274 262 251 240 229 218 213 202 178 149 123 100 82 56 33 25 16 9 5 3 1 0
The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_02_02_antineo.sas 12APR23:19:35 Output File: f_14_02_02_02_02_antineo.rtf

Overall survival

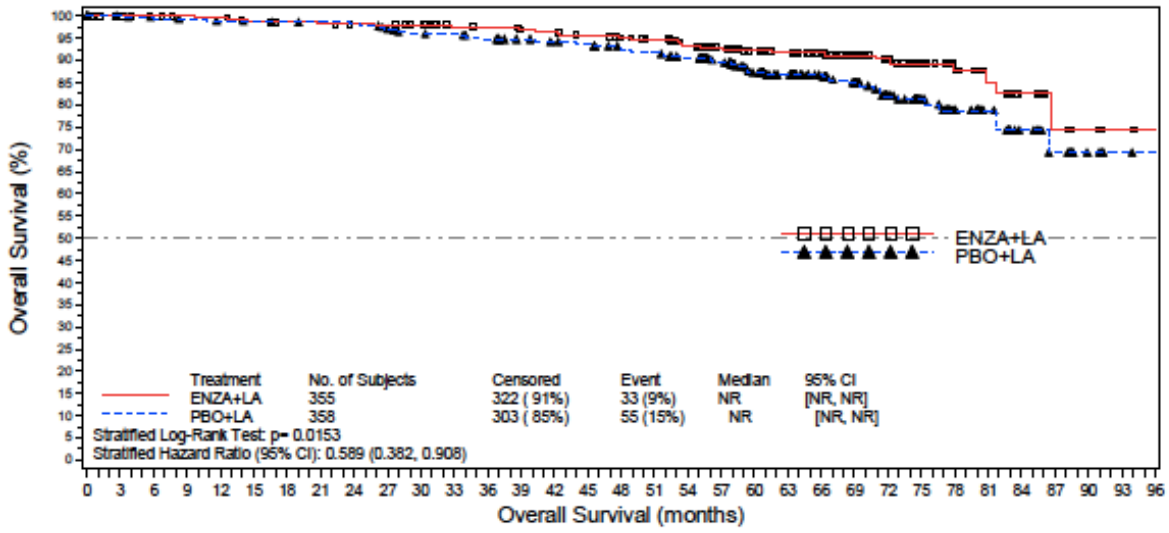
At the interim analysis, the OS data was immature, with 130 (48.0%) OS events out of the required 271 OS events in the 3 treatment groups for final OS analysis [Table 17]. The median OS was NR in any of the treatment groups. The median follow-up time of OS was 65.0 months for enzalutamide plus leuprolide, 66.2 months for placebo plus leuprolide, and 63.7 months for enzalutamide monotherapy.

Table 18. OS - Key Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Survival Status			
Death	33 (9.3%)	55 (15.4%)	42 (11.8%)
Censored†	322 (90.7%)	303 (84.6%)	313 (88.2%)
Alive at Data Analysis Cutoff Date	274 (77.2%)	257 (71.8%)	259 (73.0%)
Lost to Follow-up	3 (0.8%)	3 (0.8%)	4 (1.1%)
Withdrew Consent to be Followed	40 (11.3%)	35 (9.8%)	38 (10.7%)
Sponsor Decision	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	5 (1.4%)	8 (2.2%)	12 (3.4%)
Overall Survival Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	86.7	81.7	NR
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
P-value‡	0.0153		0.2304
Hazard Ratio (95% CI)‡	0.589 (0.382, 0.908)		0.782 (0.523, 1.170)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.997 (0.980,1.000)	0.989 (0.970,0.996)	0.997 (0.980,1.000)
Year 2 (95% CI)	0.983 (0.962,0.992)	0.983 (0.962,0.992)	0.991 (0.973,0.997)
Year 3 (95% CI)	0.977 (0.954,0.988)	0.948 (0.919,0.967)	0.968 (0.942,0.982)
Observed Follow-up Time for Censored Patients§ (in Months)			
n	322	303	313
25th Percentile	57.9	58.0	58.0
Median	63.8	63.7	63.6
75th Percentile	74.5	74.6	74.4
Min, Max	0.39,94.13	0.03,93.93	0.62,93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	58.0	58.1	58.0
Median (95% CI)	65.0 (63.5, 66.3)	66.2 (63.5, 67.0)	63.7 (63.5, 66.3)
75th Percentile	74.6	74.9	74.5

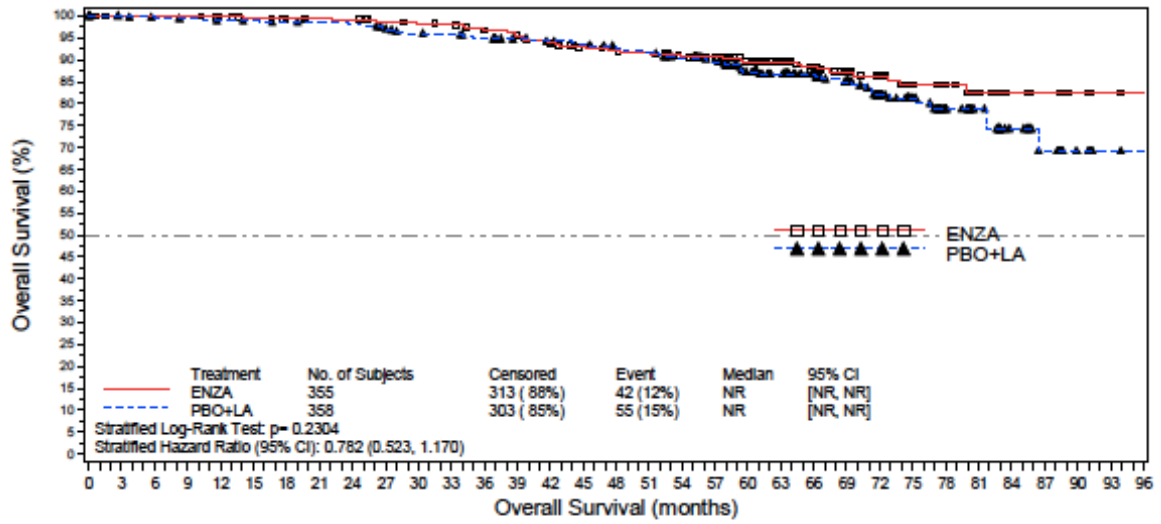
The data cut-off date is 31 Jan 2023. NR = Not Reached.
†Patients who were not known to have died at the analysis date are censored at date last know alive or data analysis cutoff date, which ever occurs first. ‡ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined
above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.
§Calculated as (date last know alive or data analysis cutoff date, whichever occurs first - randomization date + 1) / 30.4375.

Figure 11. K-M Curves for OS for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)



ENZA+LA:
Event/Cum. Events 0/0 0/0 0/0 0/0 1/1 3/4 1/5 1/6 0/6 1/7 0/7 1/8 0/8 2/10 2/12 3/15 1/16 1/17 5/22 1/23 2/25 1/26 0/26 1/27 1/28 1/29 1/30 1/31 1/32 1/33 0/33 0/33 0/33
Patients at Risk 355 352 349 347 346 341 337 336 334 333 330 321 320 316 314 309 305 301 290 258 230 191 161 121 100 72 53 34 20 9 4 2 0
PBO+LA:
Event/Cum. Events 0/0 0/0 1/1 1/2 2/4 0/4 1/5 0/5 1/6 4/10 4/14 0/14 4/18 0/18 2/20 2/22 3/25 3/28 4/32 3/35 6/41 1/42 0/42 3/45 4/49 1/50 2/52 0/52 2/54 1/55 0/55 0/55 0/55
Patients at Risk 358 354 351 349 346 345 343 342 341 335 328 327 321 316 312 309 301 298 287 259 224 192 157 131 99 71 49 35 20 13 5 1 0
The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_03_01_os.sas 15MAY23:20:53 Output File: f_14_02_02_03_01_os.rtf

Figure 12. K-M Curves for OS for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)



ENZA:
Event/Cum. Events 0/0 0/0 0/0 0/0 1/1 1/2 0/2 0/2 1/3 1/4 2/6 1/7 4/11 4/15 6/21 3/24 3/27 1/28 3/31 0/31 3/34 0/34 2/36 2/38 1/39 2/41 0/41 1/42 0/42 0/42 0/42 0/42 0/42
Patients at Risk 355 353 353 353 349 346 343 340 339 335 332 330 323 318 310 301 296 294 287 256 225 184 153 120 95 64 48 31 15 8 3 1 0
PBO+LA:
Event/Cum. Events 0/0 0/0 1/1 1/2 2/4 0/4 1/5 0/5 1/6 4/10 4/14 0/14 4/18 0/18 2/20 2/22 3/25 3/28 4/32 3/35 6/41 1/42 0/42 3/45 4/49 1/50 2/52 0/52 2/54 1/55 0/55 0/55 0/55
Patients at Risk 358 354 351 349 346 345 343 342 341 335 328 327 321 316 312 309 301 298 287 259 224 192 157 131 99 71 49 35 20 13 5 1 0
The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_03_02_os.sas 15MAY23:20:54 Output File: f_14_02_02_03_02_os.rtf

Other secondary endpoints

Time to distant metastasis

Table 19: Time to Distant Metastasis Based on BICR Assessment - Other Secondary Efficacy Analysis (ITT Population)

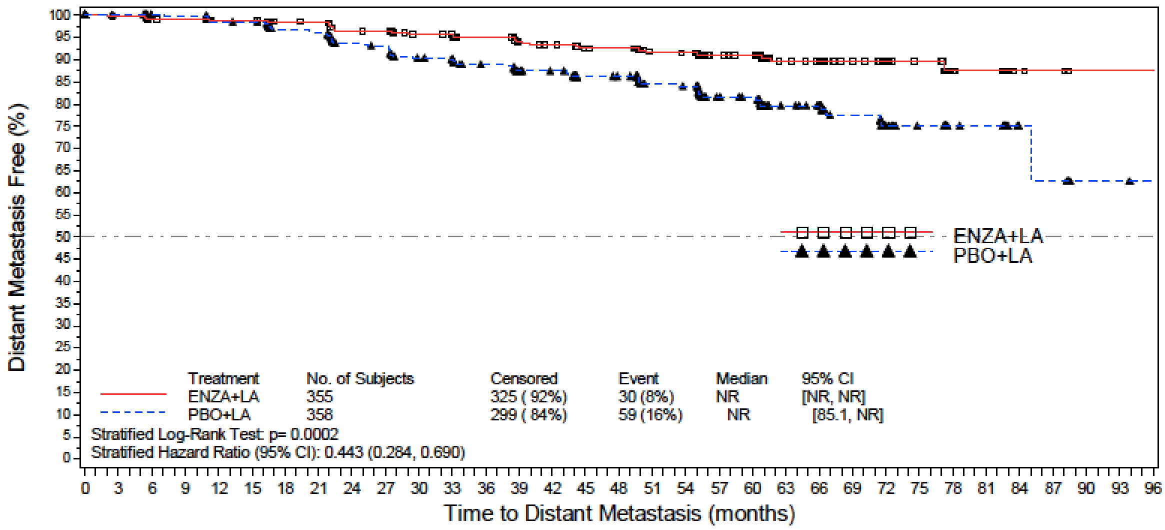
	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Distant Metastasis Status			
Distant Metastasis†	30 (8.5%)	59 (16.5%)	40 (11.3%)
Bone Progression	14 (3.9%)	29 (8.1%)	25 (7.0%)
Soft Tissue Progression	15 (4.2%)	27 (7.5%)	14 (3.9%)
Concurrent Bone and Soft Tissue Progression	1 (0.3%)	3 (0.8%)	1 (0.3%)
Distant Metastasis Status			
Censored‡	325 (91.5%)	299 (83.5%)	315 (88.7%)
No Postbaseline Assessments	11 (3.1%)	9 (2.5%)	4 (1.1%)
Metastatic Disease at Randomization	1 (0.3%)	2 (0.6%)	1 (0.3%)
Initiation of Antineoplastic Therapy	41 (11.5%)	88 (24.6%)	52 (14.6%)
Abiraterone Acetate	0 (0.0%)	5 (1.4%)	0 (0.0%)
Abiraterone Acetate + Horm	0 (0.0%)	1 (0.3%)	0 (0.0%)
Bone Targeting Agent (BTA) + Horm	0 (0.0%)	0 (0.0%)	2 (0.6%)
Cytotoxic Chemotherapy	11 (3.1%)	5 (1.4%)	4 (1.1%)
Cytotoxic Chemotherapy + Horm	0 (0.0%)	1 (0.3%)	1 (0.3%)
Cytotoxic Chemotherapy + Other	0 (0.0%)	1 (0.3%)	0 (0.0%)
Hormonal Therapy	28 (7.9%)	72 (20.1%)	44 (12.4%)
Prostate Cancer Vaccine	1 (0.3%)	0 (0.0%)	0 (0.0%)
Other Anti-Cancer Therapy	1 (0.3%)	1 (0.3%)	1 (0.3%)
2+ Missed Visits	4 (1.1%)	5 (1.4%)	4 (1.1%)
Unknown Distant Metastasis Disease Status	1 (0.3%)	0 (0.0%)	3 (0.8%)
No Distant Metastatic Disease	267 (75.2%)	195 (54.5%)	251 (70.7%)
Time to Distant Metastasis based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	NR	85.1	NR
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
P-value§	0.0002		0.0171
Hazard Ratio (95% CI)§	0.443 (0.284, 0.690)		0.614 (0.409, 0.920)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.988 (0.969, 0.996)	0.985 (0.964, 0.994)	0.988 (0.969, 0.996)
Year 2 (95% CI)	0.963 (0.936, 0.979)	0.937 (0.904, 0.959)	0.929 (0.895, 0.952)
Year 3 (95% CI)	0.950 (0.919, 0.969)	0.889 (0.848, 0.919)	0.926 (0.891, 0.950)
Observed Follow-up Time for Censored Patients¶ (in Months)			
n	325	299	315
25th Percentile	45.4	33.1	38.7

	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)
Median	60.6	55.2	60.6
75th Percentile	67.9	66.2	66.9
Min, Max	0.03, 88.41	0.03, 93.90	0.03, 88.48
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	49.6	38.5	44.1
Median (95% CI)	60.6 (60.3, 60.8)	55.6 (55.2, 60.6)	60.6 (60.3, 60.8)
75th Percentile	71.3	66.3	68.8

The data cut-off date is 31 Jan 2023. NR = Not Reached.

† Based on the earliest objective evidence of distant soft tissue metastases or metastatic bone disease by BICR.
‡ Censoring rules will follow those in the primary MFS analysis except the situation in previous footnote. § Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.
¶ Calculated as (date of last assessment showing no evidence of distant metastasis - randomization date + 1) / 30.4375.

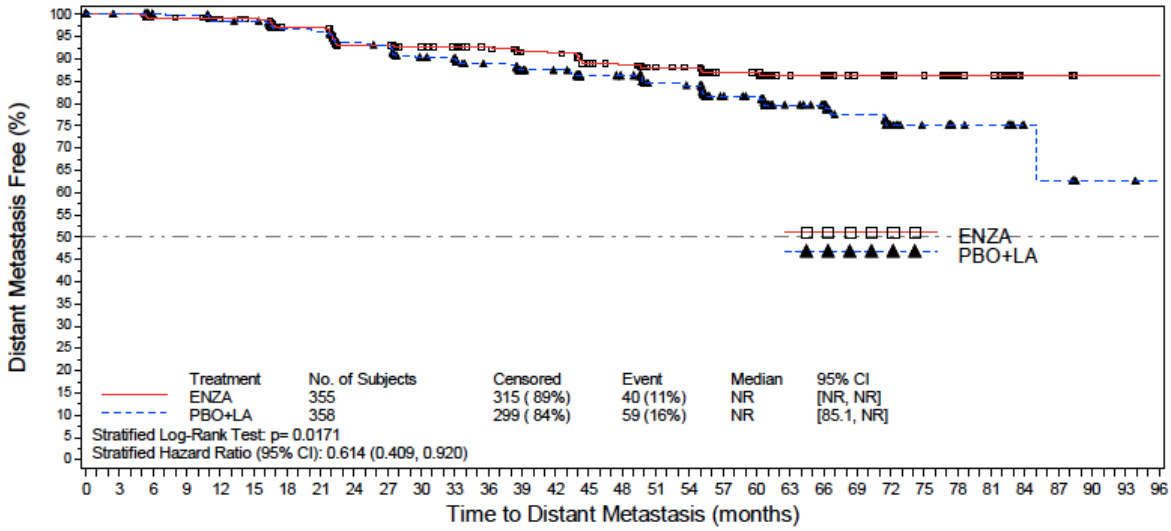
Figure 13: K-M Curves for Time to Distant Metastasis Based on BICR Review Assessment for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96
ENZA+LA:																																	
Event/Cum. Events	0/0	1/1	2/3	0/3	1/4	0/4	1/5	0/5	7/12	0/12	2/14	0/14	2/16	3/19	2/21	2/23	0/23	2/25	1/26	1/27	0/27	2/29	0/29	0/29	0/29	0/29	1/30	0/30	0/30	0/30	0/30	0/30	0/30
Patients at Risk	355	339	331	330	325	325	318	317	304	303	290	288	280	269	265	251	250	236	234	182	179	119	116	82	60	51	24	22	6	5	0	0	0
PBO+LA:																																	
Event/Cum. Events	0/0	0/0	0/0	1/1	4/5	0/5	6/11	2/13	7/20	2/22	8/30	1/31	3/34	4/38	0/38	3/41	0/41	4/45	1/46	5/51	0/51	3/54	0/54	2/56	2/58	0/58	0/58	0/58	0/58	1/59	0/59	0/59	0/59
Patients at Risk	358	344	334	333	321	320	303	301	279	276	260	257	239	227	223	207	205	187	185	142	139	92	87	66	32	27	15	14	6	5	1	1	0

The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_09_01_disticr.sas 12APR23:19:38 Output File: f_14_02_03_09_01_disticr.rtf

Figure 14. K-M Curves for Time to Distant Metastasis Based on BICR Review Assessment for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



ENZA:
Event/Cum. Events 0/0 0/0 3/3 0/3 1/4 0/4 6/10 0/10 13/23 0/23 1/24 0/24 0/24 3/27 1/28 6/34 1/35 1/36 0/36 3/39 0/39 1/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40 0/40
Patients at Risk 355 350 341 340 328 326 311 311 288 288 277 272 259 247 246 233 228 212 210 172 171 109 108 76 52 49 25 24 5 5 0 0 0
PBO+LA:
Event/Cum. Events 0/0 0/0 0/0 1/1 4/5 0/5 6/11 2/13 7/20 2/22 8/30 1/31 3/34 4/38 0/38 3/41 0/41 4/45 1/46 5/51 0/51 3/54 0/54 2/56 2/58 0/58 0/58 0/58 0/58 1/59 0/59 0/59 0/59
Patients at Risk 358 344 334 333 321 320 303 301 279 276 260 257 239 227 223 207 205 187 185 142 139 92 87 66 32 27 15 14 6 5 1 1 0
The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_09_02_distcr.sas 12APR23:19:38 Output File: f_14_02_03_09_02_distcr.rtf

Proportion of participants with undetectable PSA at 36 weeks on study treatment

The proportion of patients (95% CI) with undetectable PSA at 36 weeks on study treatment was 97.3% (95% CI: 94.9%, 98.7%) in the enzalutamide plus leuprolide group, 71.4% (95% CI: 66.3%, 76.2%) in the placebo plus leuprolide group, and 90.2% (95% CI: 86.5%, 93.2%) in the enzalutamide monotherapy group (Table 19).

Table 20. Proportion of Patients with Undetectable PSA at Week 36 – Other Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Number of Patients with PSA Values at Week 36	331 (93.2%)	336 (93.9%)	337 (94.9%)
Patients with Undetectable Prostate Specific Antigen (PSA) at Week 36	322 (97.3%)	240 (71.4%)	304 (90.2%)
Proportion (95% CI)†	97.3% (94.9%, 98.7%)	71.4% (66.3%, 76.2%)	90.2% (86.5%, 93.2%)
Difference of Proportion (95% CI)‡	25.9% (20.7%, 31.0%)		18.8% (13.0%, 24.6%)
P-value§	0.0001		0.0001

The data cut-off date is 31 Jan 2023. † Clopper-Pearson exact binomial confidence interval (CI). ‡ Proportion in ENZA+LA minus proportion in PBO+LA, or proportion in ENZA minus proportion in PBO+LA. 95% CI is based on Wald type method. § P-value is based on a Cochran-Mantel-Haenszel test stratified by screening PSA, PSADT, and prior hormonal therapy.

Proportion of participants who remain treatment-free 2 years after suspension of study treatment at week 37 due to undetectable PSA

Table 21. Proportion of Patients Who Remained Treatment Free 2 Years After Suspension of Study Treatment - Other Secondary efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Number of Patients with Treatment Suspension	321 (90.4%)	240 (67.0%)	304 (85.6%)
Remain Treatment Free at 2 Years after Treatment Suspension	111 (34.6%)	65 (27.1%)	43 (14.1%)
Proportion (95% CI)†	34.6% (29.4%, 40.1%)	27.1% (21.6%, 33.2%)	14.1% (10.4%, 18.6%)
Difference of Proportion (95% CI)‡	7.5% (-0.2%, 15.2%)		-12.9% (-19.8%, -6.1%)
P-value§	0.0439		0.0004

The data cut-off date is 31 Jan 2023.† Clopper-Pearson exact binomial confidence interval (CI).‡ Proportion in ENZA+LA minus proportion in PBO+LA, or proportion in ENZA minus proportion in PBO+LA. 95% CI is based on Wald type method.§ P-value is based on a Cochran-Mantel-Haenszel test stratified by screening PSA, PSADT, and prior hormonal therapy.

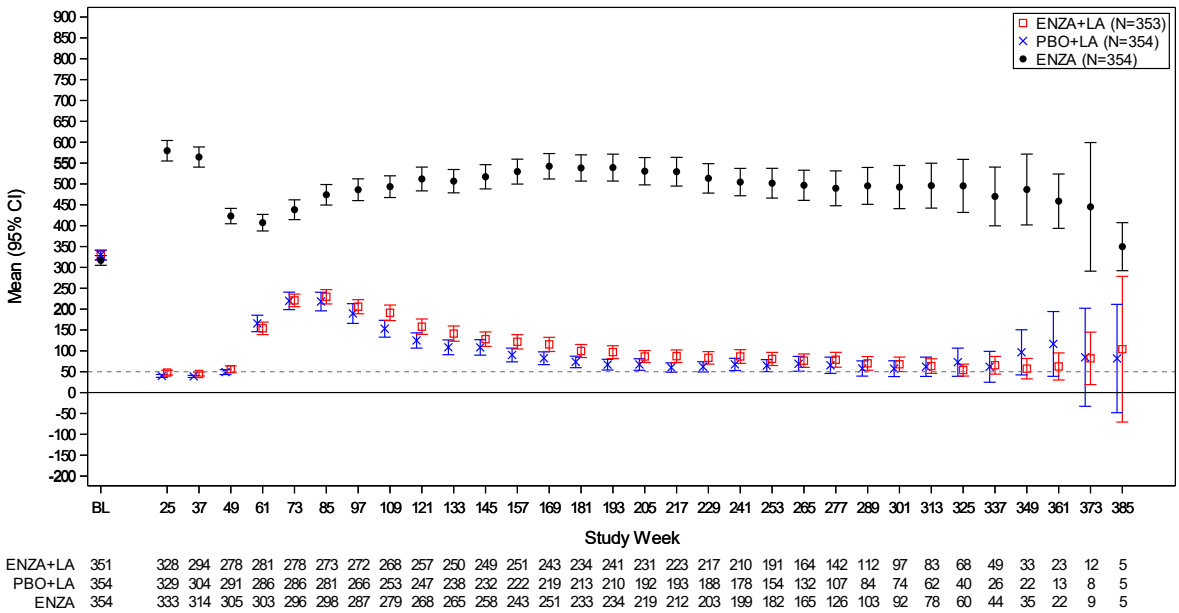
Serum testosterone in safety population

The mean baseline serum testosterone levels were comparable across the 3 treatment groups and in line with the inclusion criteria of the EMBARK protocol for serum testosterone (enzalutamide plus leuprolide: 329.3 ng/dL; placebo plus leuprolide: 329.7 ng/dL; and enzalutamide monotherapy: 316.7 ng/dL).

During therapy, leuprolide-containing groups showed a decrease in mean testosterone serum levels by week 37, whereas the enzalutamide monotherapy group showed an increase in serum testosterone levels (enzalutamide plus leuprolide: 44.5 ng/dL; placebo plus leuprolide: 38.8 ng/d; and enzalutamide monotherapy: 564.5 ng/dL) (Figure 15).

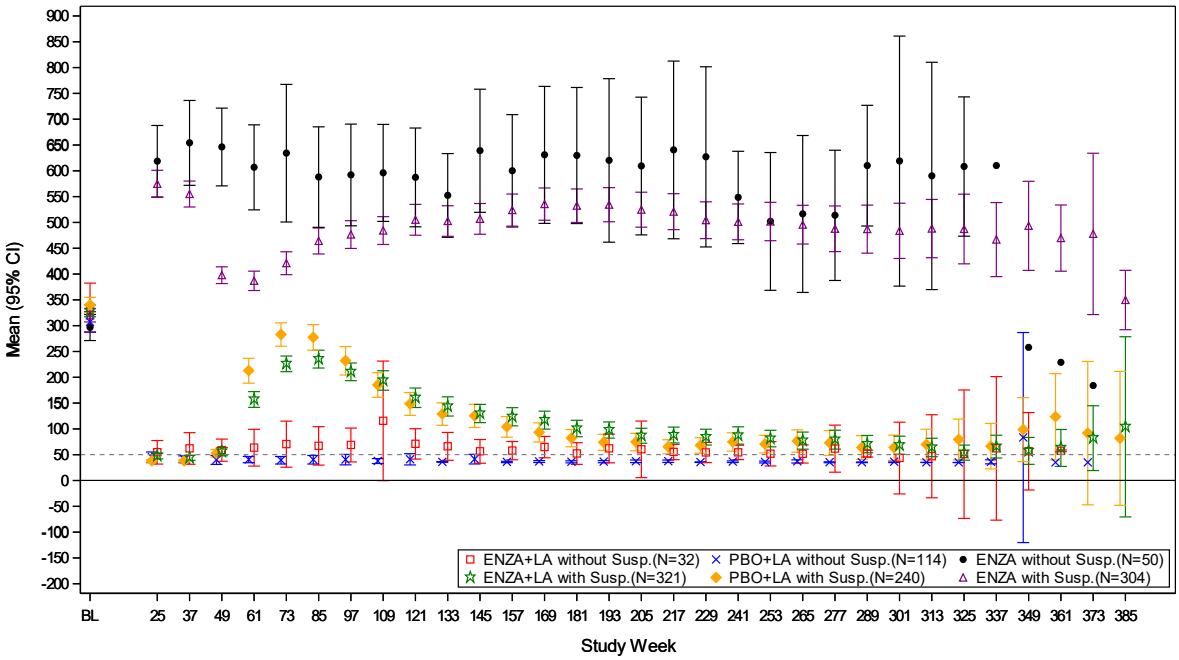
Following treatment suspension, mean serum testosterone level increased on leuprolide-containing groups (enzalutamide plus leuprolide [229.6 ng/dL] and placebo plus leuprolide [218.2 ng/dL] by week 85); in contrast mean serum testosterone level decreased following suspension of enzalutamide monotherapy (407.2 ng/dL [week 61]) (Figure 16). With continued follow-up and increasing numbers of patients undergoing treatment re-initiation mean serum testosterone levels were consistently suppressed in leuprolide containing groups and consistently elevated in enzalutamide monotherapy groups when compared to the respective mean baseline level.

Figure 15. Mean (95% CI) Testosterone (ng/dL) Levels in Patients by Visit (Safety Population)



The data cut-off date is 31 Jan 2023.

Figure 16. Mean (95%) Testosterone (ng/dL) Levels in Patients by Treatment Arm and Suspension Status by Visit (Safety Population)



The data cut-off date is 31 Jan 2023.

Proportion of participants with undetectable PSA at 2 years after suspension of study treatment at week 37 due to undetectable PSA

The proportion (95% CI) of patients with undetectable PSA 2 years after treatment suspension at week 37 due to undetectable PSA was 16.8% (95% CI: 12.9%, 21.4%) in the enzalutamide plus leuprolide

group, 9.6% (95% CI: 6.2%, 14.0%) in the placebo plus leuprolide group, and 4.6% (95% CI: 2.5%, 7.6%) in the enzalutamide monotherapy group [Table 22].

Table 22: Proportion of Patients with Undetectable PSA 2 Years After Suspension of Study Treatment – Other Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Number of Patients with Treatment Suspension	321 (90.4%)	240 (67.0%)	304 (85.6%)
Remain Treatment-free at 2 Years after Treatment Suspension	54 (16.8%)	23 (9.6%)	14 (4.6%)
Proportion (95% CI)†	16.8% (12.9%, 21.4%)	9.6% (6.2%, 14.0%)	4.6% (2.5%, 7.6%)
Difference of Proportion (95% CI)‡	7.2% (1.7%, 12.8%)		-5.0% (-9.4%, -0.6%)
P-value§	0.0089		0.0326

The data cut-off date is 31 Jan 2023.† Clopper-Pearson exact binomial confidence interval (CI).‡ Proportion in ENZA+LA minus proportion in PBO+LA, or proportion in ENZA minus proportion in PBO+LA. 95% CI is based on Wald type method.§ P-value is based on a Cochran-Mantel-Haenszel test stratified by screening PSA, PSADT, and prior hormonal therapy.

Time to resumption of any hormonal therapy

Table 23. Time to Resumption of Any Hormonal Therapy - Other Secondary Efficacy Analysis (ITT Population)

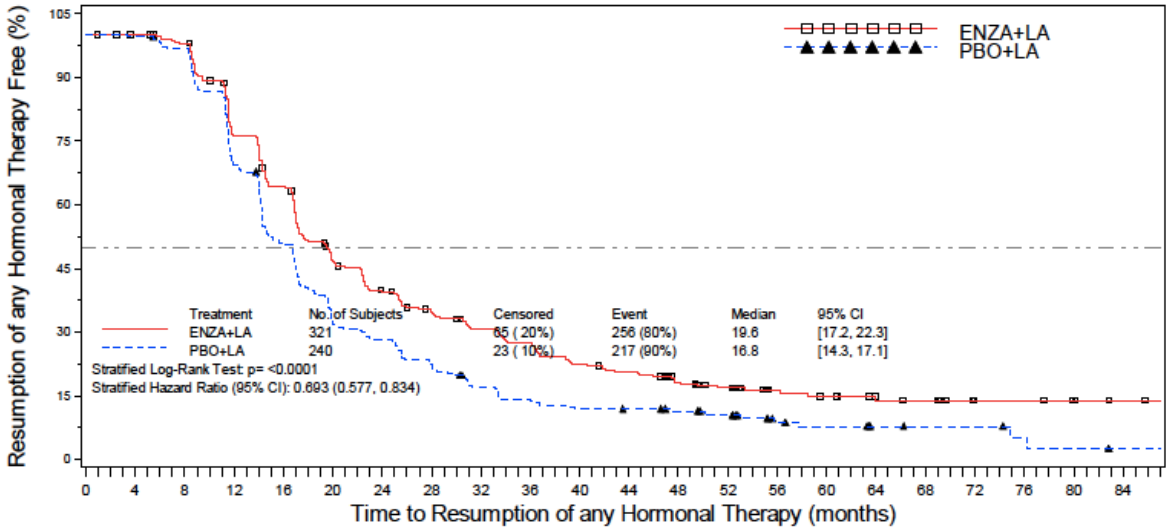
	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Number of Patients with Treatment Suspension	321 (90.4%)	240 (67.0%)	304 (85.6%)
Status of Time to Resumption of any Hormonal Therapy			
Event†	256 (79.8%)	217 (90.4%)	279 (91.8%)
Censored‡	65 (20.2%)	23 (9.6%)	25 (8.2%)
Time to Resumption of any Hormonal Therapy Based on K-M Estimates (in Months)			
n	321	240	304
25th Percentile	13.9	11.5	6.0
Median (95% CI)	19.6 (17.2, 22.3)	16.8 (14.3, 17.1)	10.5 (8.9, 11.5)
75th Percentile	36.6	25.6	17.3
P-value§	< 0.0001		< 0.0001
Hazard Ratio (95% CI)§	0.693 (0.577, 0.834)		1.655 (1.381, 1.984)
Probability of Being Event Free Based on K-M Estimates at:			

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Year 1 (95% CI)	0.764 (0.713, 0.807)	0.695 (0.632, 0.749)	0.383 (0.328, 0.438)
Year 2 (95% CI)	0.395 (0.341, 0.449)	0.282 (0.226, 0.340)	0.156 (0.117, 0.200)
Year 3 (95% CI)	0.275 (0.226, 0.327)	0.136 (0.096, 0.184)	0.084 (0.056, 0.119)
Observed Follow-up Time for Censored Patients¶ (in Months)			
n	65	23	25
25th Percentile	27.5	46.6	6.0
Median	50.2	52.6	52.6
75th Percentile	60.8	63.3	57.9
Min, Max	0.95, 85.82	5.45, 82.83	0.03, 77.08
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	321	240	304
25th Percentile	49.4	52.4	52.7
Median (95% CI)	55.0 (52.5, 60.8)	55.6 (52.6, 63.5)	55.3 (52.9, 63.8)
75th Percentile	69.0	66.2	66.7

The data cut-off date is 31 Jan 2023.

NR = Not Reached.The time to resumption of any hormonal therapy is defined as the time between the date of treatment suspension at week 37 due to undetectable PSA and the date that hormonal therapy is restarted.†
Based on the hormonal therapy restarted after treatment suspension at week 37 due to undetectable PSA‡Patients without observed re sumption of any hormonal therapy at the time of analysis will be censored at the date of last visit.§ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above
and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.¶Calculated as (date of last assessment with out resumption of any hormonal therapy prior to analysis data cutoff date - randomization date + 1) / 30.4375.

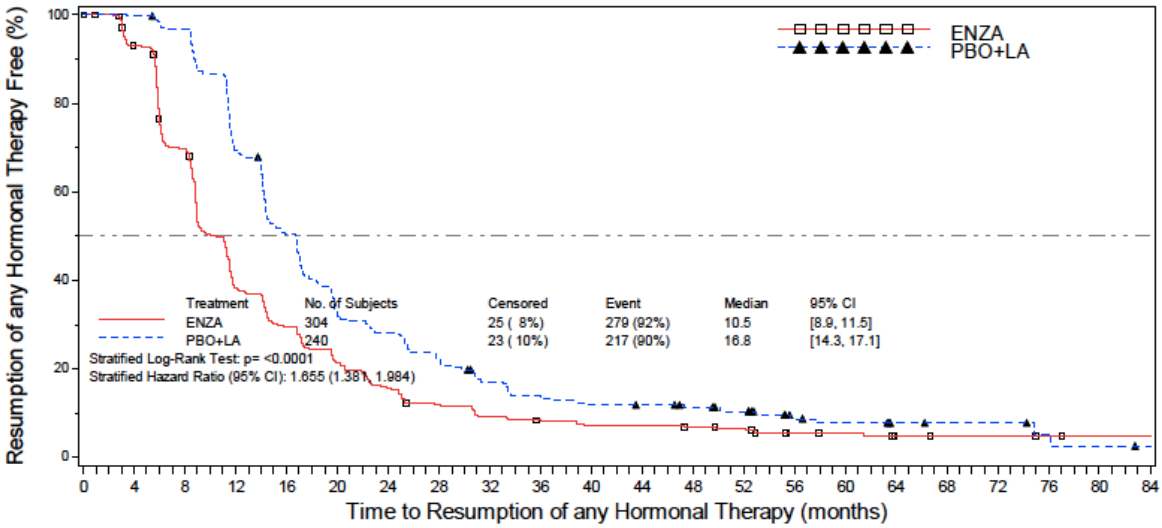
Figure 17. K-M Curves for Time to Resumption of any Hormonal Therapy for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups – Other Secondary Efficacy Analysis (ITT Population)



ENZA+LA:																					
Event/Cum. Events	0/0	0/0	6/6	68/74	38/112	54/166	22/188	14/202	12/214	9/223	15/238	5/243	6/249	3/252	1/253	2/255	1/256	0/256	0/256	0/256	0/256
Patients at Risk	321	318	310	239	200	143	119	102	88	79	64	58	44	36	23	20	14	12	5	5	3	1
PBO+LA:																					
Event/Cum. Events	0/0	1/1	7/8	65/73	45/118	41/159	12/171	14/185	12/197	8/205	4/209	0/209	1/210	2/212	2/214	1/215	0/215	0/215	0/215	1/216	1/217	0/217
Patients at Risk	240	239	231	166	120	79	67	53	39	31	27	26	23	19	10	8	5	4	4	2	1	0

The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_02_01_hormres.sas 12APR23:20:03 Output File: f_14_02_03_02_01_hormres.rtf

Figure 18. K-M Curves for Time to Resumption of any Hormonal Therapy for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



ENZA:																					
Event/Cum. Events	0/0	21/21	70/91	92/183	26/209	24/233	17/250	11/261	7/268	3/271	3/274	0/274	1/275	1/276	2/278	0/278	1/279	0/279	0/279	0/279	0/279
Patients at Risk	304	278	206	113	87	63	46	34	27	23	20	20	18	16	8	7	4	3	3	2	0	0
PBO+LA:																					
Event/Cum. Events	0/0	1/1	7/8	65/73	45/118	41/159	12/171	14/185	12/197	8/205	4/209	0/209	1/210	2/212	2/214	1/215	0/215	0/215	0/215	1/216	1/217	0/217
Patients at Risk	240	239	231	166	120	79	67	53	39	31	27	26	23	19	10	8	5	4	4	2	1	0

The data cut-off date is 31JAN2023.
NR=Not Reached
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_02_02_hormres.sas 12APR23:20:05 Output File: f_14_02_03_02_02_hormres.rtf

Time to castration resistance

A total of 14 (3.9%) patients in the enzalutamide plus leuprolide group and 120 (33.5%) patients in the placebo plus leuprolide group developed castration resistance as of the data cut-off date.

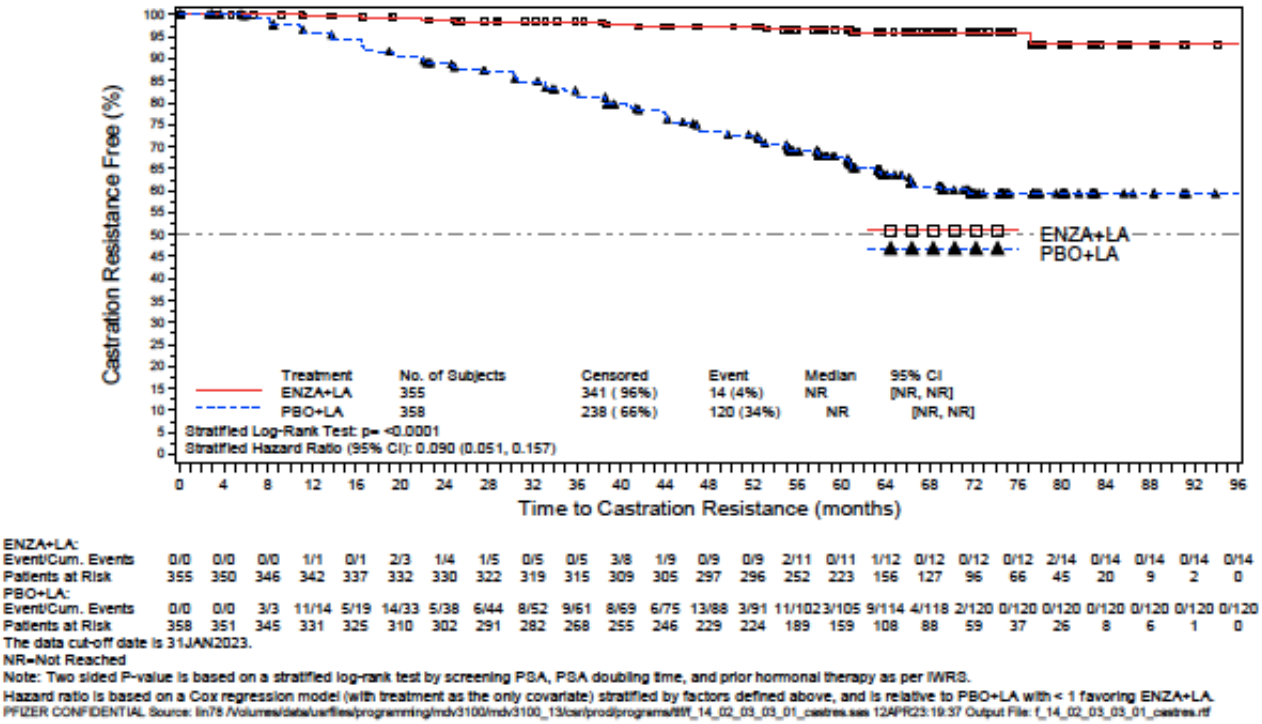
Table 24. Time to Castration Resistance for Patients Receiving Leuprolide Treatment – Other Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**
Status of Time to Castration Resistance		
Event†	14 (3.9%)	120 (33.5%)
Censored	341 (96.1%)	238 (66.5%)
Time to Castration Resistance Based on K-M Estimates (in Months)		
n	355	358
25th Percentile	NR	46.9
Median (95% CI)	NR (NR, NR)	NR (NR, NR)
75th Percentile	NR	NR
p-value‡	< 0.0001	
Hazard Ratio (95% CI)‡	0.090 (0.051, 0.157)	
Probability of Being Event Free Based on K-M Estimates at:		
Year 1 (95% CI)	0.997 (0.980, 1.000)	0.960 (0.933, 0.976)
Year 2 (95% CI)	0.988 (0.969, 0.996)	0.890 (0.852, 0.919)
Year 3 (95% CI)	0.985 (0.965, 0.994)	0.821 (0.776, 0.858)
Observed Follow-up Time for Censored Patients§ (in Months)		
n	341	238
25th Percentile	55.4	55.3
Median	63.5	63.3
75th Percentile	74.2	71.9
Min, Max	0.03, 94.13	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)		
n	355	358
25th Percentile	55.4	57.8
Median (95% CI)	63.5 (61.4, 66.1)	63.5 (63.2, 66.3)
75th Percentile	74.4	74.3

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Based on the first occurrence of radiographic disease progression by BICR, PSA progression, or SSE whichever occurs first with castrate levels of testosterone (< 50 ng/dL).‡ Two-sided P-value is based on a

stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA.§ Calculated as (date of last assessment showing no evidence of castration resistance prior to analysis data cutoff date - randomization date + 1) / 30.4375.

Figure 19. K-M Curves for Time to Castration Resistance for Participants Receiving Leuprolide Treatment – Other Secondary Efficacy Analysis (ITT Population)



Time to symptomatic progression

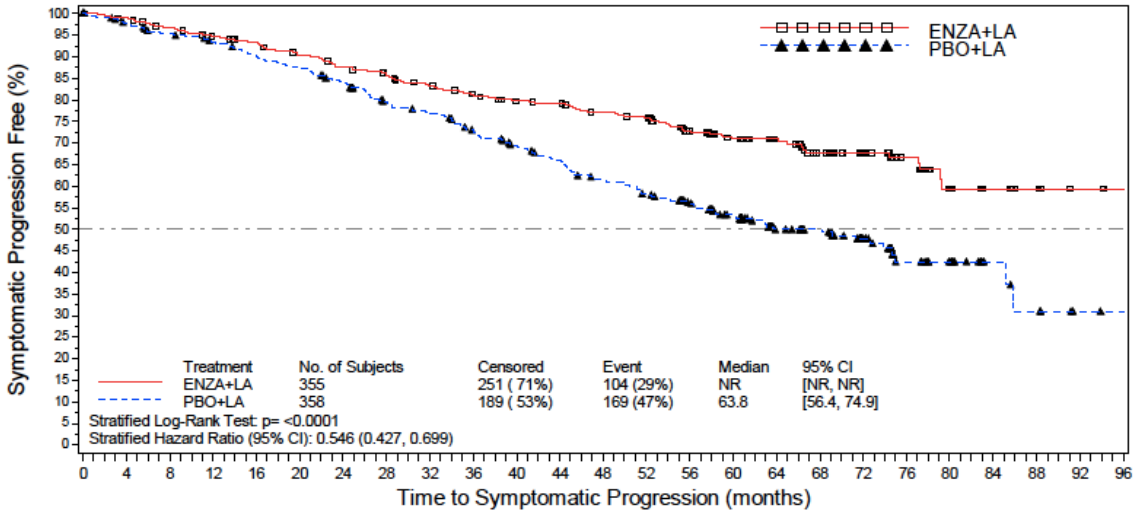
Table 25. Time to Symptomatic Progression - Other Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of Time to Symptomatic Progression			
Events†	104 (29.3%)	169 (47.2%)	117 (33.0%)
New Systemic Antineoplastic Therapy	46 (13.0%)	115 (32.1%)	77 (21.7%)
Opiate Use	52 (14.6%)	43 (12.0%)	35 (9.9%)
Skeletal-related Event	6 (1.7%)	11 (3.1%)	5 (1.4%)
Censored	251 (70.7%)	189 (52.8%)	238 (67.0%)
No first symptomatic Progression - last visit date	250 (70.4%)	187 (52.2%)	237 (66.8%)
No first symptomatic Progression - Randomization date	1 (0.3%)	2 (0.6%)	1 (0.3%)
Time to Symptomatic Progression based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	52.5	34.1	44.2
Median (95% CI)	NR (NR, NR)	63.8 (56.4, 74.9)	NR (83.6, NR)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
75th Percentile	NR	NR	NR
p-value‡	< 0.0001		< 0.0001
Hazard Ratio (95% CI)‡	0.546 (0.427, 0.699)		0.619 (0.488, 0.785)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.945 (0.916, 0.965)	0.934 (0.903, 0.956)	0.960 (0.934, 0.976)
Year 2 (95% CI)	0.877 (0.837, 0.908)	0.839 (0.795, 0.873)	0.867 (0.826, 0.898)
Year 3 (95% CI)	0.813 (0.767, 0.851)	0.730 (0.680, 0.774)	0.778 (0.730, 0.819)
Observed Follow-up Time for Censored Patients§ (in Months)			
n	251	189	238
25th Percentile	55.4	55.2	57.9
Median	63.5	61.8	63.5
75th Percentile	72.1	71.8	74.4
Min, Max	0.03, 94.13	0.03, 93.90	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	57.9	58.0	58.0
Median (95% CI)	63.7 (63.5, 66.3)	63.6 (63.4, 66.5)	63.6 (63.5, 66.4)
75th Percentile	74.5	74.3	74.6

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Based on the earliest contributing event (skeletal-related event, new systemic antineoplastic therapy, opiate use, surgical intervention or radiation therapy).‡ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.
§Calculated as (date of last assessment showing no symptomatic progression prior to analysis data cutoff date - randomization date + 1) / 30.4375.

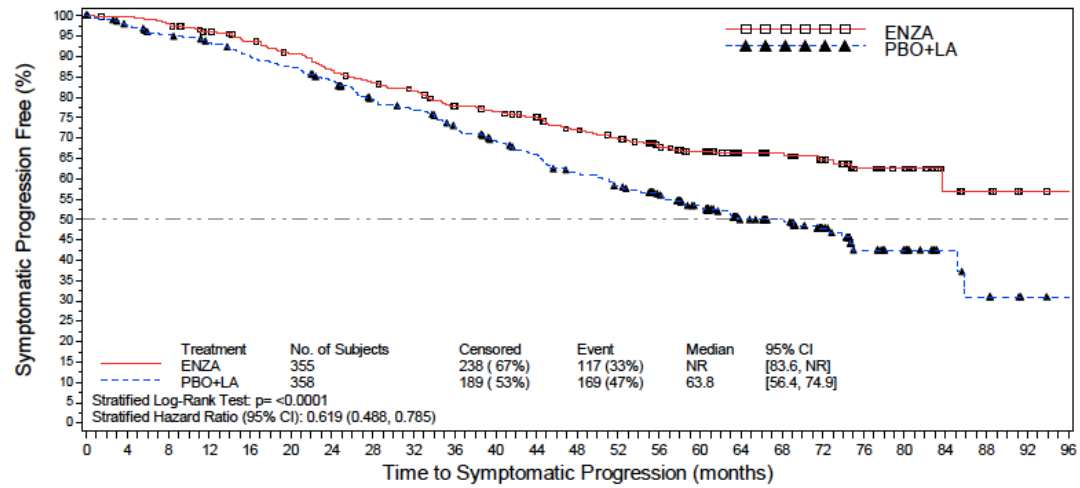
Figure 20. K-M Curves for Time to Symptomatic Progression for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



ENZA+LA:																								
Event/Cum. Events	0/0	4/4	7/11	8/19	4/23	10/33	9/42	6/48	9/57	6/63	5/68	2/70	6/76	4/80	9/89	5/94	0/94	5/99	0/99	1/100	4/104	0/104	0/104	0/104	0/104
Patients at Risk	355	346	336	325	316	303	293	282	270	261	252	249	240	235	198	173	122	96	72	47	26	14	7	2	0
PBO+LA:																									
Event/Cum. Events	0/0	8/8	9/17	6/23	11/34	10/44	12/56	14/70	10/80	12/92	12/104	11/115	15/130	9/139	6/145	8/153	7/160	0/160	3/163	4/167	0/167	0/167	2/169	0/169	0/169
Patients at Risk	358	344	332	323	311	301	286	265	254	238	221	208	191	181	160	128	87	75	48	25	19	8	5	1	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/ttf/f_14_02_03_07_01_ttsympd.sas 12APR23:19:37 Output File: f_14_02_03_07_01_ttsympd.rtf

Figure 21. K-M Curves for Time to Symptomatic Progression for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



ENZA:																								
Event/Cum. Events	0/0	1/1	6/7	7/14	8/22	11/33	13/46	11/57	7/64	12/76	4/80	5/85	10/95	6/101	7/108	3/111	1/112	0/112	2/114	2/116	0/116	1/117	0/117	0/117	0/117
Patients at Risk	355	352	346	333	322	309	296	284	275	259	252	244	229	221	191	170	114	98	72	48	35	10	5	1	0
PBO+LA:																									
Event/Cum. Events	0/0	8/8	9/17	6/23	11/34	10/44	12/56	14/70	10/80	12/92	12/104	11/115	15/130	9/139	6/145	8/153	7/160	0/160	3/163	4/167	0/167	0/167	2/169	0/169	0/169
Patients at Risk	358	344	332	323	311	301	286	265	254	238	221	208	191	181	160	128	87	75	48	25	19	8	5	1	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/ttf/f_14_02_03_07_02_ttsympd.sas 12APR23:19:37 Output File: f_14_02_03_07_02_ttsympd.rtf

Time to first symptomatic skeletal event

Table 26. Time to First SSE - Other Secondary Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of Time to Symptomatic Skeletal Event			

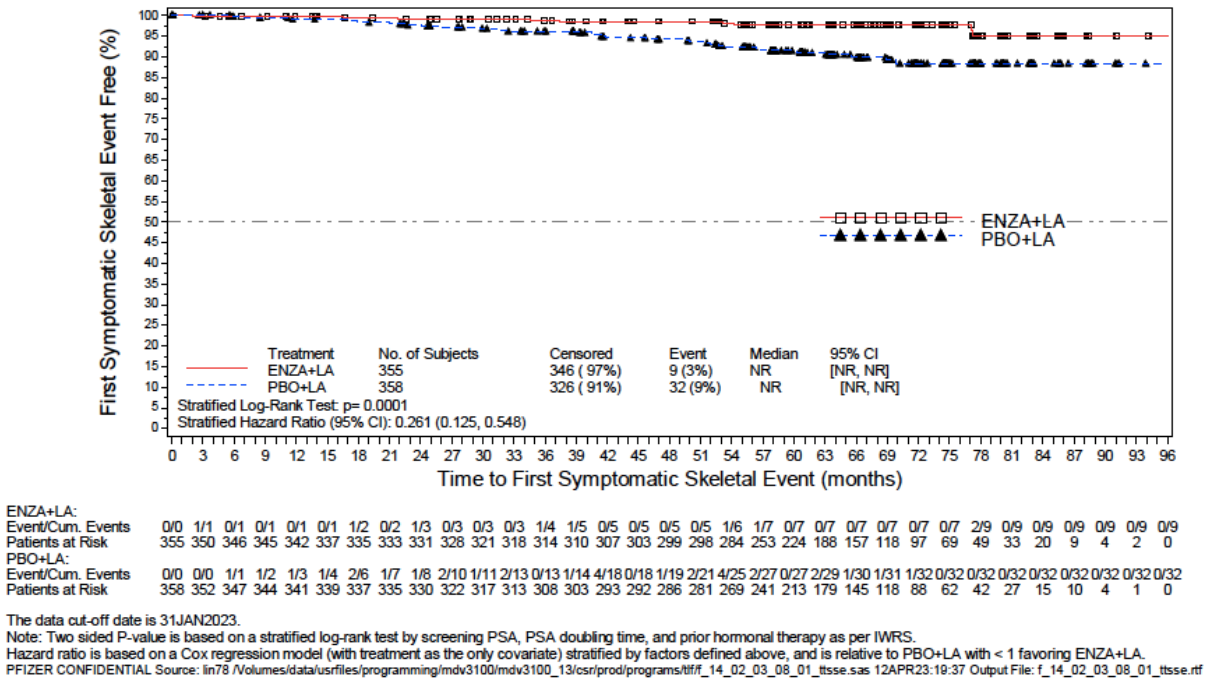
	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Events†	9 (2.5%)	32 (8.9%)	14 (3.9%)
Radiation Therapy to Bone	3 (0.8%)	14 (3.9%)	5 (1.4%)
Surgery to Bone	0 (0.0%)	1 (0.3%)	0 (0.0%)
Pathological Bone Fracture	5 (1.4%)	2 (0.6%)	3 (0.8%)
Spinal Cord Compression	0 (0.0%)	2 (0.6%)	1 (0.3%)
Initiation/Change of Antineoplastic Therapy to treat Bone Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Opiate use due to Bone Pain	1 (0.3%)	12 (3.4%)	5 (1.4%)
Censored	346 (97.5%)	326 (91.1%)	341 (96.1%)
No First Symptomatic Skeletal Event - Last Visit Date	345 (97.2%)	324 (90.5%)	340 (95.8%)
No First Symptomatic Skeletal Event - Randomization date	1 (0.3%)	2 (0.6%)	1 (0.3%)
Time to Symptomatic Skeletal Event Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	NR	NR	NR
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
p-value‡	0.0001		0.0057
Hazard Ratio (95% CI)‡	0.261 (0.125, 0.548)		0.423 (0.226, 0.794)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.997 (0.980, 1.000)	0.991 (0.973, 0.997)	0.997 (0.980, 1.000)
Year 2 (95% CI)	0.991 (0.973, 0.997)	0.977 (0.954, 0.988)	0.994 (0.977, 0.999)
Year 3 (95% CI)	0.988 (0.969, 0.996)	0.962 (0.935, 0.978)	0.982 (0.961, 0.992)
Observed Follow-up Time for Censored Patients§ (in Months)			
n	346	326	341
25th Percentile	55.4	55.4	55.3
Median	63.5	63.5	63.5

	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)
75th Percentile	74.2	74.4	72.3
Min, Max	0.03, 94.13	0.03, 93.90	0.03, 93.90
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	55.4	55.6	55.3
Median (95% CI)	63.5 (61.4, 66.1)	63.5 (61.8, 66.1)	63.5 (61.2, 63.6)
75th Percentile	74.4	74.4	72.4

The data cut-off date is 31 Jan 2023.

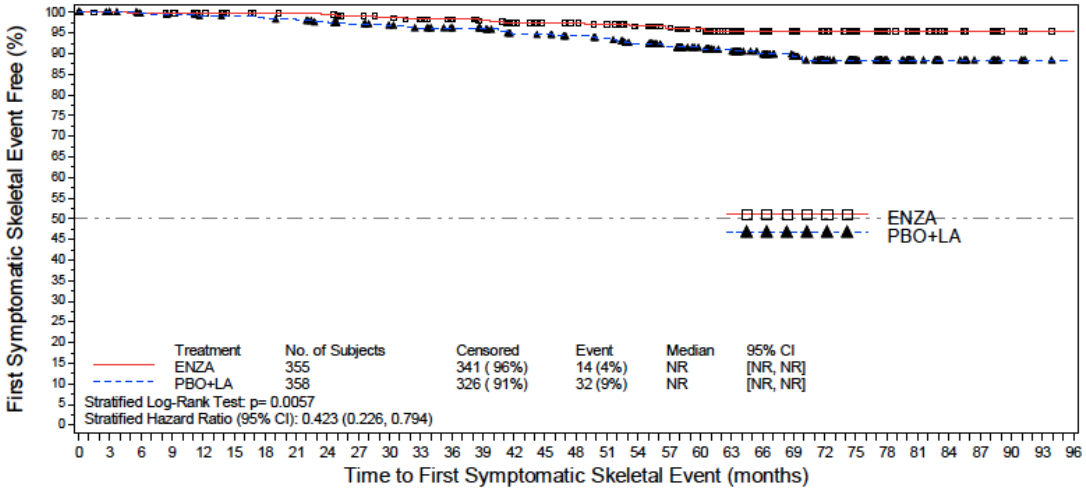
NR = Not Reached.† Based on first symptomatic skeletal event in CRF form‡ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.§Calculated as (date of last assessment sho wing no symptomatic skeletal event prior to analysis data cutoff date - randomization date + 1) / 30.4375.

Figure 22. K-M Curves for Time to First SSE for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_08_01_ttsse.sas 12APR23:19:37 Output File: f_14_02_03_08_01_ttsse.rtf

Figure 23. K-M Curves for Time to First SSE for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Other Secondary Efficacy Analysis (ITT Population)



ENZA:
Event/Cum. Events 0/0 0/0 1/1 0/1 0/1 0/1 0/1 0/1 1/2 1/3 1/4 2/6 0/6 1/7 2/9 0/9 0/9 1/10 1/11 1/12 1/13 1/14 0/14 0/14 0/14 0/14 0/14 0/14 0/14 0/14 0/14 0/14
Patients at Risk 355 353 352 351 345 341 339 338 337 332 329 324 316 309 301 292 290 286 277 246 221 177 145 114 90 62 47 30 15 8 3 1 0
PBO+LA:
Event/Cum. Events 0/0 0/0 1/1 1/2 1/3 1/4 2/6 1/7 1/8 2/10 1/11 2/13 0/13 1/14 4/18 0/18 1/19 2/21 4/25 2/27 0/27 2/29 1/30 1/31 1/32 0/32 0/32 0/32 0/32 0/32 0/32 0/32 0/32
Patients at Risk 358 352 347 344 341 339 337 335 330 322 317 313 308 303 293 292 286 281 269 241 213 179 145 118 88 62 42 27 15 10 4 1 0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: lin78 /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_03_08_02_ttsse.sas 12APR23:19:37 Output File: f_14_02_03_08_02_ttsse.rtf

Exploratory endpoint

PFS2

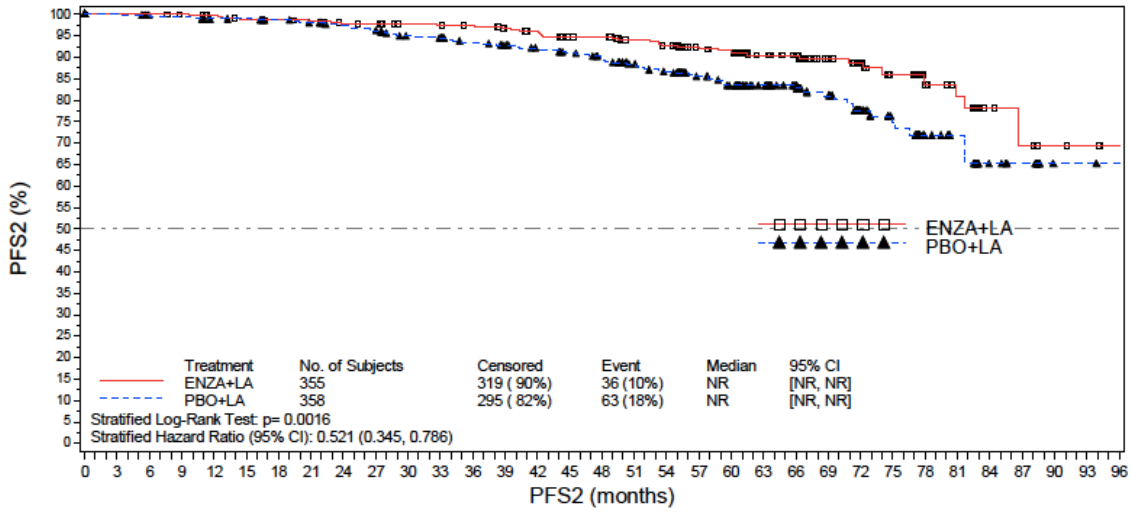
Table 27. PFS2 Based on Investigator Review – Exploratory Endpoint Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of PFS2 Follow-up			
Events†	36 (10.1%)	63 (17.6%)	48 (13.5%)
Progression by investigator	8 (2.3%)	18 (5.0%)	17 (4.8%)
PSA Progression	4 (1.1%)	6 (1.7%)	5 (1.4%)
Progression by Imaging	3 (0.8%)	12 (3.4%)	8 (2.3%)
Clinical Progression	1 (0.3%)	0 (0.0%)	4 (1.1%)
Death	28 (7.9%)	45 (12.6%)	31 (8.7%)
Censored‡	319 (89.9%)	295 (82.4%)	307 (86.5%)
No Metastatic Disease or Death	293 (82.5%)	235 (65.6%)	282 (79.4%)
Start of New Antineoplastic Therapy	2 (0.6%)	7 (2.0%)	6 (1.7%)
Withdrawal of Consent	1 (0.3%)	4 (1.1%)	3 (0.8%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ongoing Without PFS2 Event	23 (6.5%)	49 (13.7%)	16 (4.5%)
PFS2 Based on K-M Estimates (in Months)			

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
n	355	358	355
25th Percentile	86.7	75.0	NR
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
75th Percentile	NR	NR	NR
P-value§	0.0016		0.1121
Hazard Ratio (95% CI)§	0.521 (0.345, 0.786)		0.739 (0.507, 1.077)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.997 (0.979, 1.000)	0.988 (0.970, 0.996)	0.997 (0.980, 1.000)
Year 2 (95% CI)	0.976 (0.953, 0.988)	0.974 (0.950, 0.986)	0.991 (0.973, 0.997)
Year 3 (95% CI)	0.973 (0.949, 0.986)	0.934 (0.901, 0.956)	0.960 (0.932, 0.977)
Observed Follow-up Time for Censored Patients¶ (in Months)			
n	319	295	307
25th Percentile	55.1	55.0	55.1
Median	60.8	60.7	60.8
75th Percentile	71.8	71.8	71.7
Min, Max	0.03, 94.13	0.03, 93.90	0.03, 88.48

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Based on the earliest contributing event after first PD (investigator assessed clinical progression, radiographic progression or PSA progression) or death due to any cause, whichever occurred first.‡
Patients who do not meet event criteria are censored based on hierarchy in SAP§ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.¶
Calculated as (date of censoring - randomization date + 1) / 30.4375.

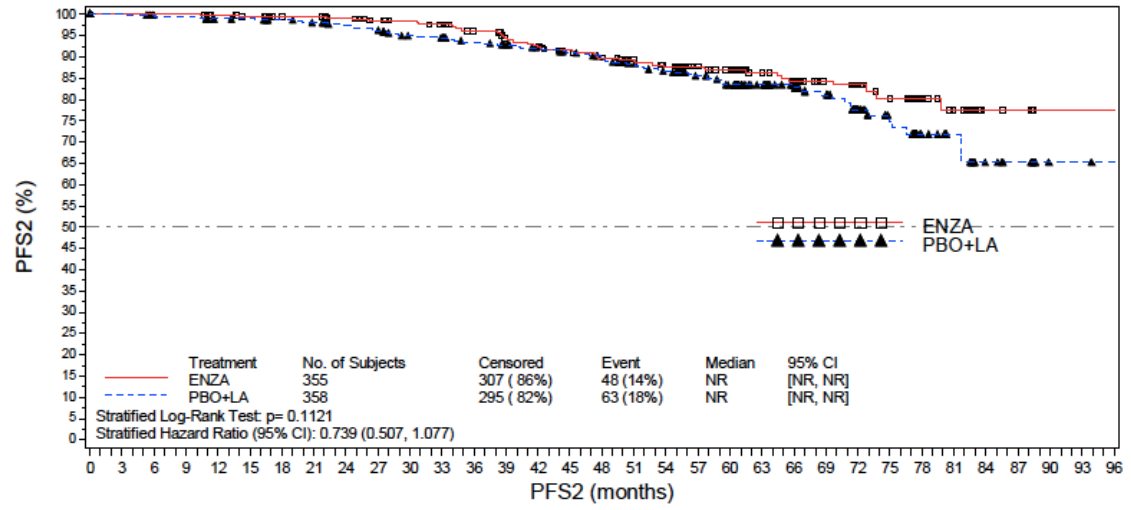
Figure 24. K-M Curves for PFS2 Based on Investigator Review for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups – Exploratory Endpoint Analysis (ITT Population)



ENZA+LA:
Event/Cum. Events 0/0 0/0 0/0 0/0 1/1 3/4 1/5 1/6 2/8 0/8 0/8 1/9 0/9 2/11 2/13 4/17 0/17 2/19 4/23 1/24 3/27 1/28 0/28 1/29 1/30 2/32 1/33 1/34 1/35 1/36 0/36 0/36 0/36
Patients at Risk 355 345 343 341 337 333 329 327 320 319 311 310 307 300 296 283 282 272 267 213 208 151 143 98 75 59 34 29 10 8 3 2 0
PBO+LA:
Event/Cum. Events 0/0 0/0 1/1 1/2 2/4 0/4 1/5 2/7 2/9 4/13 4/17 2/19 3/22 2/24 3/27 3/30 4/34 3/37 5/42 3/45 5/50 0/50 0/50 3/53 4/57 1/58 3/61 0/61 2/63 0/63 0/63 0/63 0/63
Patients at Risk 358 350 346 345 340 339 333 329 323 319 308 305 293 288 281 274 266 253 245 201 191 140 126 98 63 51 28 22 12 9 1 1 0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_04_01_01_pfs2.sas 15MAY23:21:11 Output File: f_14_02_04_01_01_pfs2.rtf

Figure 25. K-M Curves for PFS2 Based on Investigator Review for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Exploratory Endpoint Analysis (ITT Population)



ENZA:
Event/Cum. Events 0/0 0/0 0/0 0/0 1/1 1/2 0/2 0/2 1/3 2/5 1/6 2/8 5/13 5/18 6/24 3/27 5/32 1/33 5/38 0/38 2/40 1/41 3/44 0/44 1/45 2/47 0/47 1/48 0/48 0/48 0/48 0/48 0/48
Patients at Risk 355 352 349 349 343 339 332 332 326 320 316 312 300 290 284 271 265 254 247 206 198 134 128 92 63 53 31 26 7 6 0 0 0
PBO+LA:
Event/Cum. Events 0/0 0/0 1/1 1/2 2/4 0/4 1/5 2/7 2/9 4/13 4/17 2/19 3/22 2/24 3/27 3/30 4/34 3/37 5/42 3/45 5/50 0/50 0/50 3/53 4/57 1/58 3/61 0/61 2/63 0/63 0/63 0/63 0/63
Patients at Risk 358 350 346 345 340 339 333 329 323 319 308 305 293 288 281 274 266 253 245 201 191 140 126 98 63 51 28 22 12 9 1 1 0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_04_01_02_pfs2.sas 15MAY23:21:10 Output File: f_14_02_04_01_02_pfs2.rtf

Efficacy results related to PROs and Quality of Life

Time to clinically relevant pain progression

Time to clinically relevant pain progression was defined as the time from randomization to onset of pain progression, where pain progression is defined as a 2-point or more increase from baseline in the BPI-SF question 3 score.

A total of 228 (64.2%) patients in the enzalutamide plus leuprolide group, 217 (60.6%) patients in the placebo plus leuprolide group, and 229 (64.5%) patients in the enzalutamide monotherapy group had clinically relevant pain progression as of the data cutoff date (Table 28).

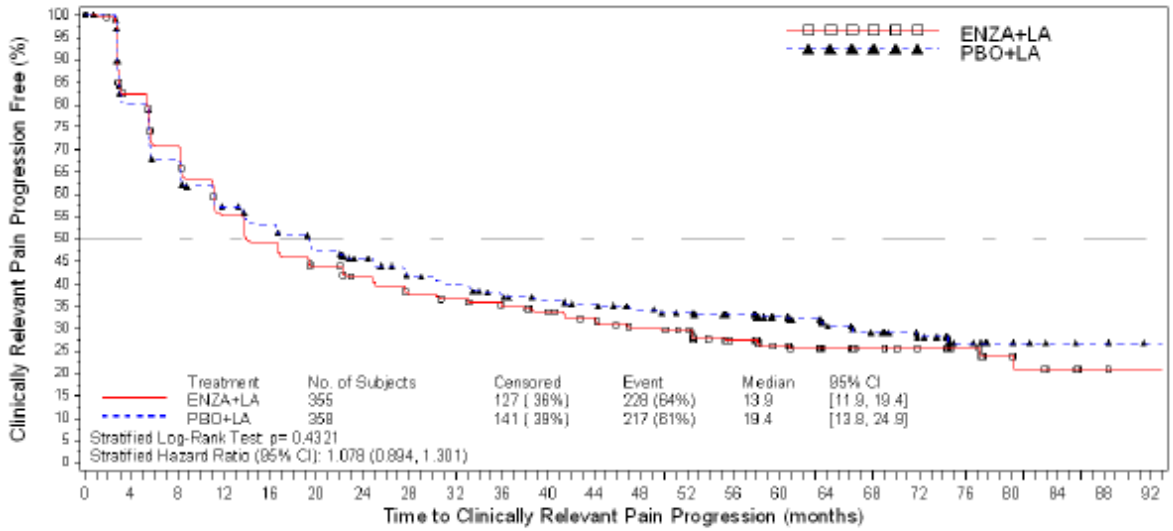
Table 28. Time to Clinically Relevant Pain Progression - PRO Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of Clinically Relevant Pain Progression			
Event†	228 (64.2%)	217 (60.6%)	229 (64.5%)
Censored	127 (35.8%)	141 (39.4%)	126 (35.5%)
Time to Clinically Relevant Pain Progression Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	5.6	5.6	5.6
Median (95% CI)	13.9 (11.9, 19.4)	19.4 (13.8, 24.9)	16.6 (12.3, 19.4)
75th Percentile	77.3	NR	63.7
P-value‡	0.4321		0.3702
Hazard Ratio (95% CI)‡	1.078 (0.894, 1.301)		1.090 (0.904, 1.314)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.553 (0.496, 0.606)	0.573 (0.517, 0.625)	0.555 (0.499, 0.608)
Year 2 (95% CI)	0.417 (0.361, 0.471)	0.457 (0.401, 0.511)	0.410 (0.355, 0.463)
Year 3 (95% CI)	0.352 (0.299, 0.406)	0.374 (0.320, 0.428)	0.341 (0.288, 0.394)
Observed Follow-up Time for Censored Patients§ (in Months)			
n	127	141	126
25th Percentile	0.0	5.8	3.9
Median	52.4	52.7	49.7
75th Percentile	66.2	66.3	63.2
Min, Max	0.03, 88.34	0.03, 91.37	0.03, 91.24
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	45.8	41.4	44.2
Median (95% CI)	59.4 (57.9, 63.5)	59.4 (57.9, 63.5)	58.0 (55.3, 60.8)
75th Percentile	71.8	73.5	69.0

The data cut-off date is 31 Jan 2023.

NR = Not Reached.† Clinically relevant pain progression is defined as a 2-point or greater increase from baseline in the BPI-SF question 3.‡ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above
and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.§
Calculated as (date of last pain assessment prior to analysis data cutoff date - randomization date + 1) / 30.4375.

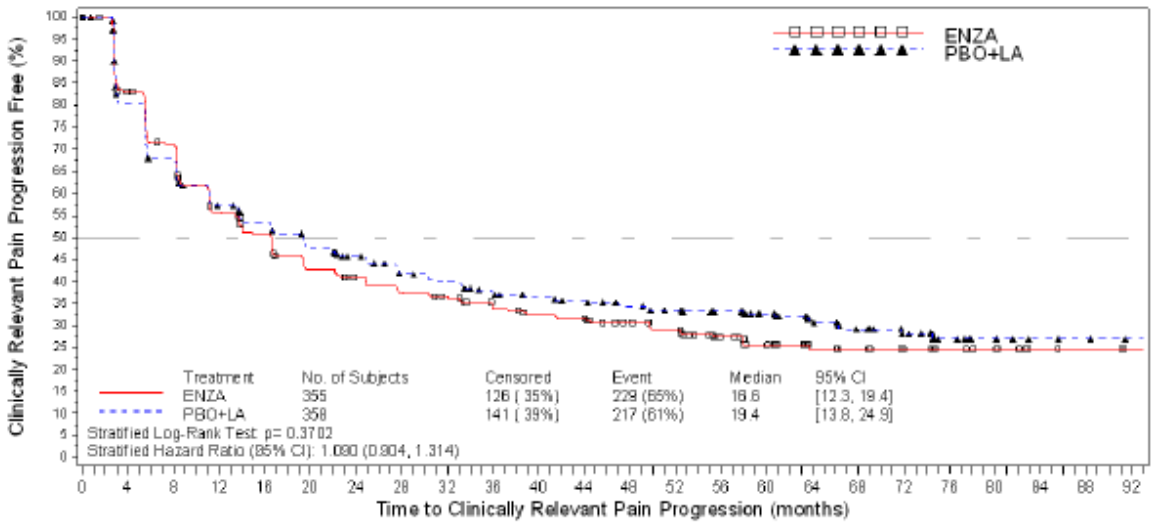
Figure 26. K-M Curves for Time to Clinically Relevant Pain Progression for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups – Other Secondary Efficacy Analysis (ITT Population)



ENZA+LA:																									
Event/Cum. Events	0/0	56/56	37/93	49/141	19/160	16/176	7/183	12/195	3/198	4/202	4/206	4/210	6/216	1/217	6/223	2/225	1/226	0/226	0/226	0/226	1/227	1/228	0/228	0/228
Patients at Risk	355	261	222	171	152	134	124	111	107	101	95	88	79	76	57	46	34	27	22	18	11	3	1	0
PBO+LA:																								
Event/Cum. Events	0/0	65/65	40/105	33/138	13/151	18/169	5/174	11/185	6/191	7/198	3/201	2/203	3/206	2/208	1/209	1/210	3/213	2/215	1/216	1/217	0/217	0/217	0/217	0/217
Patients at Risk	358	258	217	181	166	146	136	121	114	104	98	94	87	82	71	58	44	36	27	15	8	3	2	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA+LA.

Figure 27: K-M Curves for Time to Clinically Relevant Pain Progression for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Other Secondary Efficacy Analysis (ITT Population)



ENZA:																									
Event/Cum. Events	0/0	55/55	38/93	50/143	15/158	25/183	5/188	10/198	3/201	7/208	4/212	3/215	2/217	4/221	4/225	3/228	1/229	0/229	0/229	0/229	0/229	0/229	0/229	0/229
Patients at Risk	355	268	228	175	157	130	121	111	106	94	88	85	77	70	54	44	25	23	17	14	12	3	2	0
PBO+LA:																								
Event/Cum. Events	0/0	65/65	40/105	33/138	13/151	18/169	5/174	11/185	6/191	7/198	3/201	2/203	3/206	2/208	1/209	1/210	3/213	2/215	1/216	1/217	0/217	0/217	0/217	0/217
Patients at Risk	358	258	217	181	166	146	136	121	114	104	98	94	87	82	71	58	44	36	27	15	8	3	2	0

The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.

Time to deterioration in FACT-P Total Score

The time to deterioration of the FACT-P total score was defined as the time from randomization to first assessment with at least a 10-point decrease from baseline in the FACT-P total score for each patient.

A total of 257 (72.4%) patients in the enzalutamide plus leuprolide group, 248 (69.3%) patients in the placebo plus leuprolide group, and 263 (74.1%) patients in the enzalutamide monotherapy group had first deterioration in FACT-P total score as of the data cutoff date (Table 29)

Table 29. Time to First Deterioration of the FACT-P Total Score - PRO Efficacy Analysis (ITT Population)

	ENZA + LA (N = 355)	**PBO + LA (N = 358)**	**ENZA (N = 355)**
Status of First Deterioration of FACT-P			
Event†	257 (72.4%)	248 (69.3%)	263 (74.1%)
Censored‡	98 (27.6%)	110 (30.7%)	92 (25.9%)
Time to First Deterioration of FACT-P Based on K-M Estimates (in Months)			
n	355	358	355
25th Percentile	2.9	5.4	2.9
Median (95% CI)	8.3 (5.7, 11.1)	11.1 (8.3, 14.0)	8.4 (5.8, 13.0)
75th Percentile	44.1	52.7	38.8
P-value§	0.1567		0.0855
Hazard Ratio (95% CI)§	1.138 (0.954, 1.357)		1.168 (0.981, 1.391)
Probability of Being Event Free Based on K-M Estimates at:			
Year 1 (95% CI)	0.414 (0.359, 0.467)	0.482 (0.426, 0.535)	0.450 (0.395, 0.503)
Year 2 (95% CI)	0.340 (0.288, 0.392)	0.353 (0.302, 0.406)	0.340 (0.288, 0.392)
Year 3 (95% CI)	0.282 (0.233, 0.333)	0.291 (0.242, 0.341)	0.266 (0.218, 0.316)
Observed Follow-up Time for Censored Patients¶ (in Months)			
n	98	110	92
25th Percentile	0.0	0.8	0.0
Median	46.9	51.1	35.1
75th Percentile	63.4	63.5	60.8
Min, Max	0.03, 88.34	0.03, 93.90	0.03, 85.52

	ENZA + LA (N = 355)	PBO + LA (N = 358)	ENZA (N = 355)
Follow-up Time Based on Reverse K-M Estimates for All Patients (in Months)			
n	355	358	355
25th Percentile	49.7	41.4	44.0
Median (95% CI)	60.8 (58.0, 63.7)	60.7 (58.2, 63.4)	60.7 (55.9, 63.5)
75th Percentile	71.8	71.8	71.8

The data cut-off date is 31 Jan 2023.NR = Not Reached.† Deterioration of FACT-P is defined as at least 10 point decrease from baseline for the total score.‡ Patients who have not had deterioration at the time of analysis data cutoff are censored at date of last assessment showing no deterioration. Patients with no baseline or postbaseline score assessments are censored at randomization.§ Two-sided P-value is based on a stratified log-rank test by screening PSA, PSADT, and prior hormonal therapy. Hazard ratio is based on a Cox regression model stratified by factors defined above and is relative to PBO+LA with < 1 favoring ENZA+LA and PBO+LA with < 1 favoring ENZA.¶ Calculated as (date of last assessment prior to analysis data cutoff date - randomization date + 1) / 30.4375.

Figure 28. K-M Curves for Time to Deterioration of the FACT-P Total Score for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups (ITT Population)

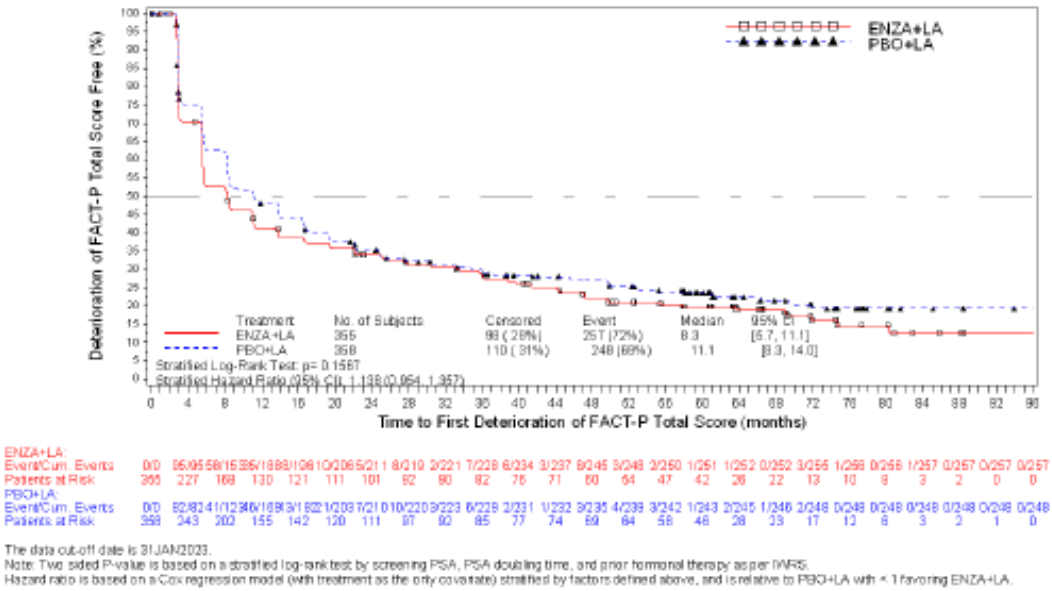
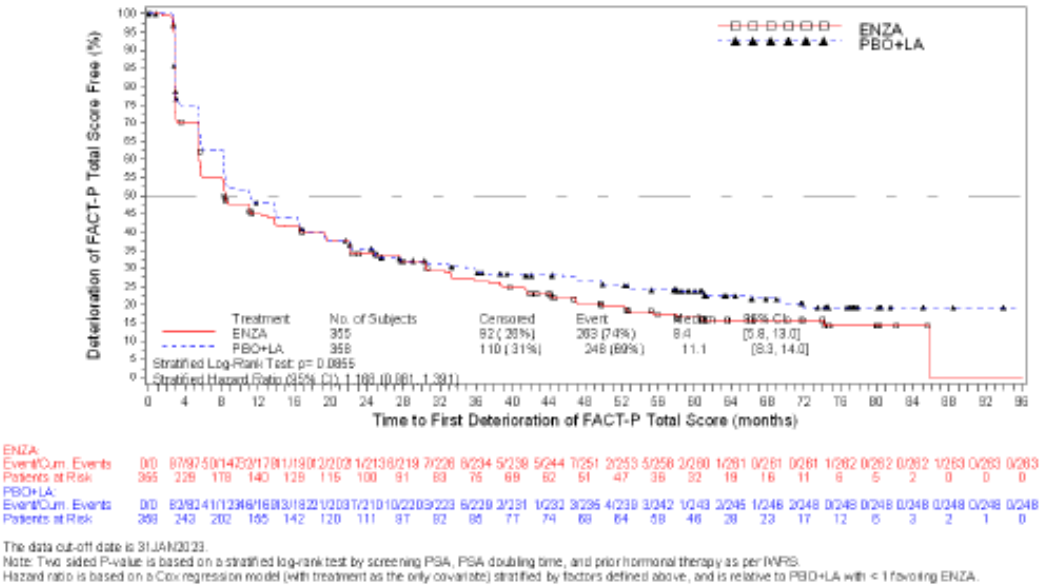


Figure 29. K-M Curves for Time to First Deterioration of the FACT-P Total Score for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups (ITT Population)



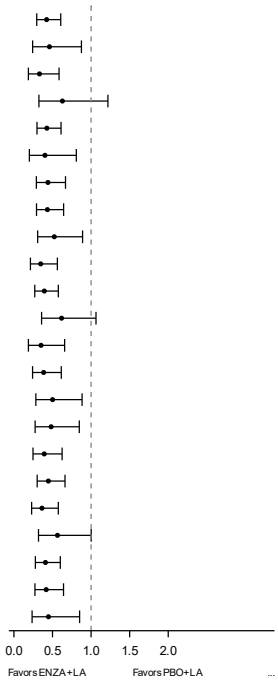
The data cut-off date is 31JAN2023.
Note: Two sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy as per IWRS.
Hazard ratio is based on a Cox regression model (with treatment as the only covariate) stratified by factors defined above, and is relative to PBO+LA with < 1 favoring ENZA.

Ancillary analyses

Subgroup analyses

Figure 30. Forest Plot for MFS by BICR for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Primary Efficacy Subgroup Analysis (ITT Population)

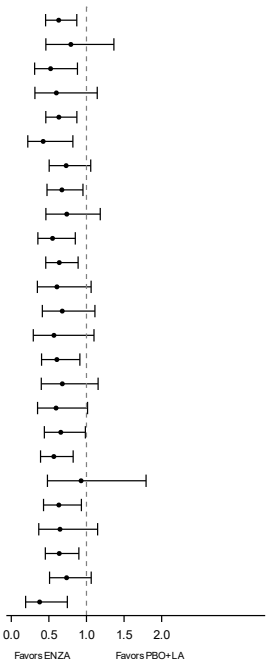
Subgroup	Number of Patients ENZA+LA / PBO+LA	Number of Events ENZA+LA / PBO+LA	Hazard Ratio for MFS (95% CI)
All Patients	355 / 358	45 / 92	0.424 (0.296,0.607)
PSA Doubling Time (<=3 Months)	69 / 80	14 / 30	0.461 (0.242,0.875)
PSA Doubling Time (>3 to <=6 Months)	187 / 142	18 / 35	0.331 (0.187,0.585)
PSA Doubling Time (>6 to <=9 Months)	98 / 135	13 / 27	0.628 (0.324,1.218)
Baseline Use of a Bone Targeting Agent (No)	355 / 358	45 / 92	0.427 (0.299,0.610)
Baseline Age Category (<65 Years)	81 / 91	11 / 28	0.402 (0.200,0.809)
Baseline Age Category (>=65 Years)	274 / 267	34 / 64	0.441 (0.291,0.668)
Race (White)	293 / 301	37 / 75	0.434 (0.293,0.644)
Body Mass Index Calculated from Height and Weight (<=Median)	173 / 179	21 / 39	0.523 (0.308,0.890)
Body Mass Index Calculated from Height and Weight (>Median)	180 / 175	24 / 53	0.347 (0.214,0.563)
ECOG Performance Status at Baseline (0)	328 / 336	39 / 87	0.394 (0.270,0.575)
Geographic Region (North America)	144 / 137	22 / 32	0.618 (0.358,1.064)
Geographic Region (Europe)	130 / 128	14 / 33	0.351 (0.188,0.657)
Total Gleason Score at Baseline (<=7) at Diagnosis	234 / 244	25 / 61	0.385 (0.242,0.614)
Total Gleason Score at Baseline (>=8) at Diagnosis	120 / 113	20 / 30	0.501 (0.284,0.883)
Prior Hormonal Therapy (Yes)	107 / 113	19 / 34	0.482 (0.275,0.847)
Prior Hormonal Therapy (No)	248 / 245	26 / 58	0.393 (0.247,0.624)
Prior Radiation Therapy (Yes)	265 / 283	37 / 76	0.447 (0.301,0.662)
Prior Prostatectomy (Yes)	269 / 254	26 / 61	0.363 (0.230,0.575)
Prior Prostatectomy (No)	86 / 104	19 / 31	0.565 (0.319,1.001)
History of Cardiovascular Disease (No)	313 / 316	38 / 81	0.409 (0.278,0.601)
PSA Value at Baseline (<=10 ng/mL)	278 / 273	31 / 64	0.419 (0.272,0.643)
PSA Value at Baseline (>10 ng/mL)	77 / 83	14 / 28	0.448 (0.235,0.851)



The data cut-off date is 31 Jan 2023.If the subgroups are too small (< 10 events), the analyses would not be provided.Hazard ratio and its 95% CI for subgroups are based on unstratified Cox regression model. Hazard ratio and its 95% CI for all patients are based on a stratified Cox regression model stratified by randomization stratification factors.

Figure 31. Forest Plot for MFS by BICR for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups – Key Secondary Subgroup Analysis (ITT Population)

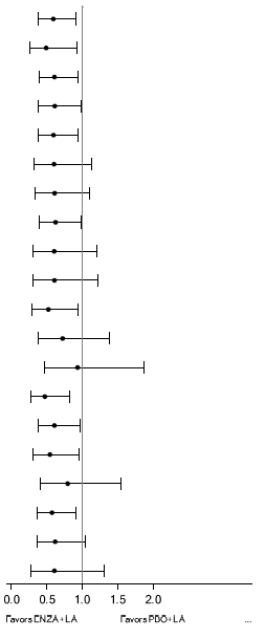
Subgroup	Number of Patients ENZA / PBO+LA	Number of Events ENZA / PBO+LA	Hazard Ratio for MFS	(95% CI)
All Patients	355 / 358	63 / 92		0.631 (0.456,0.871)
PSA Doubling Time (<=3 Months)	76 / 80	24 / 30		0.792 (0.460,1.365)
PSA Doubling Time (>3 to <=6 Months)	164 / 142	24 / 35		0.523 (0.311,0.880)
PSA Doubling Time (>6 to <=9 Months)	114 / 135	14 / 27		0.599 (0.314,1.143)
Baseline Use of a Bone Targeting Agent (No)	355 / 358	63 / 92		0.633 (0.459,0.872)
Baseline Age Category (<65 Years)	91 / 91	13 / 28		0.424 (0.220,0.819)
Baseline Age Category (>=65 Years)	264 / 267	50 / 64		0.730 (0.504,1.057)
Race (White)	295 / 301	55 / 75		0.673 (0.475,0.953)
Body Mass Index Calculated from Height and Weight (<=Median)	185 / 179	31 / 39		0.738 (0.460,1.183)
Body Mass Index Calculated from Height and Weight (>Median)	169 / 175	32 / 53		0.549 (0.354,0.851)
ECOG Performance Status at Baseline (0)	321 / 336	59 / 87		0.638 (0.459,0.889)
Geographic Region (North America)	133 / 137	20 / 32		0.607 (0.347,1.062)
Geographic Region (Europe)	146 / 128	30 / 33		0.678 (0.413,1.112)
Geographic Region (Rest of the World)	76 / 93	13 / 27		0.567 (0.293,1.100)
Total Gleason Score at Baseline (<=7) at Diagnosis	239 / 244	37 / 61		0.606 (0.403,0.912)
Total Gleason Score at Baseline (>=8) at Diagnosis	111 / 113	25 / 30		0.679 (0.399,1.155)
Prior Hormonal Therapy (Yes)	112 / 113	23 / 34		0.595 (0.349,1.014)
Prior Hormonal Therapy (No)	243 / 245	40 / 58		0.658 (0.440,0.985)
Prior Radiation Therapy (Yes)	256 / 283	43 / 76		0.566 (0.389,0.823)
Prior Radiation Therapy (No)	99 / 75	20 / 16		0.928 (0.481,1.793)
Prior Prostatectomy (Yes)	265 / 254	44 / 61		0.632 (0.429,0.933)
Prior Prostatectomy (No)	90 / 104	19 / 31		0.648 (0.366,1.148)
History of Cardiovascular Disease (No)	308 / 316	55 / 81		0.638 (0.453,0.899)
PSA Value at Baseline (<=10 ng/mL)	272 / 273	51 / 64		0.736 (0.509,1.063)
PSA Value at Baseline (>10 ng/mL)	82 / 83	12 / 28		0.377 (0.191,0.746)



The data cut-off date is 31 Jan 2023.If the subgroups are too small (< 10 events), the analyses would not be provided.Hazard ratio and its 95% CI for subgroups are based on unstratified Cox regression model. Hazard ratio and its 95% CI for all patients are based on a stratified Cox regression model stratified by randomization stratification factors.

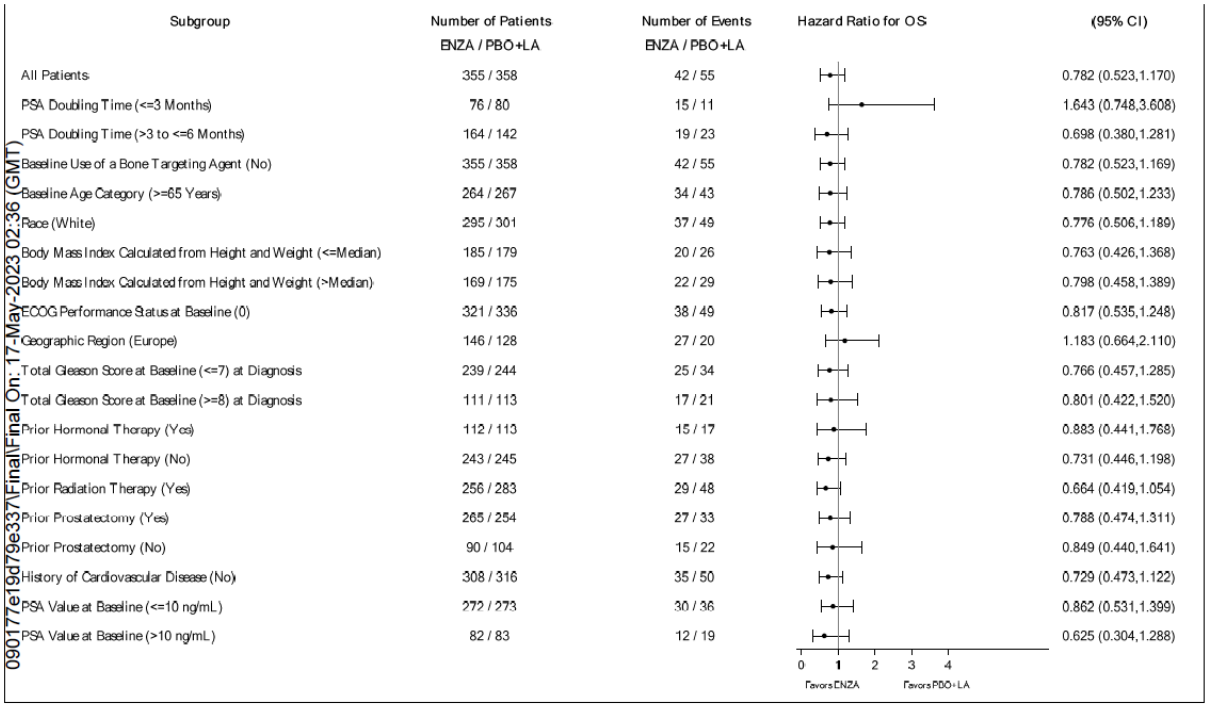
Figure 32. Forest Plot of Overall Survival for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)

Subgroup	Number of Patients ENZA+LA / PBO+LA	Number of Events ENZA+LA / PBO+LA	Hazard Ratio for OS	(95% CI)
All Patients	355 / 358	33 / 55		0.589 (0.382,0.908)
PSA Doubling Time (>3 to <=6 Months)	187 / 142	16 / 23		0.488 (0.256,0.928)
Baseline Use of a Bone Targeting Agent (No)	355 / 358	33 / 55		0.605 (0.393,0.932)
Baseline Age Category (>=65 Years)	274 / 267	28 / 43		0.608 (0.378,0.980)
Race (White)	293 / 301	28 / 49		0.591 (0.372,0.941)
Body Mass Index Calculated from Height and Weight (<=Median)	173 / 179	15 / 26		0.598 (0.317,1.130)
Body Mass Index Calculated from Height and Weight (>Median)	180 / 175	18 / 29		0.608 (0.338,1.095)
ECOG Performance Status at Baseline (0)	328 / 336	30 / 49		0.621 (0.394,0.978)
Geographic Region (North America)	144 / 137	13 / 22		0.602 (0.303,1.196)
Geographic Region (Europe)	130 / 128	13 / 20		0.605 (0.301,1.216)
Total Gleason Score at Baseline (<=7) at Diagnosis	234 / 244	17 / 34		0.519 (0.290,0.929)
Total Gleason Score at Baseline (>=8) at Diagnosis	120 / 113	16 / 21		0.720 (0.375,1.381)
Prior Hormonal Therapy (Yes)	107 / 113	15 / 17		0.932 (0.465,1.866)
Prior Hormonal Therapy (No)	248 / 245	18 / 38		0.469 (0.268,0.822)
Prior Radiation Therapy (Yes)	265 / 283	27 / 48		0.604 (0.377,0.968)
Prior Prostatectomy (Yes)	269 / 254	19 / 33		0.541 (0.308,0.952)
Prior Prostatectomy (No)	86 / 104	14 / 22		0.791 (0.404,1.547)
History of Cardiovascular Disease (No)	313 / 316	28 / 50		0.571 (0.360,0.907)
PSA Value at Baseline (<=10 ng/mL)	278 / 273	23 / 36		0.614 (0.364,1.036)
PSA Value at Baseline (>10 ng/mL)	77 / 83	10 / 19		0.604 (0.280,1.302)



The data cut-off date is 31JAN2023.
If the subgroups are too small (<10 events), the analyses would not be provided.
Hazard ratio and its 95% CI for subgroups are based on unstratified Cox regression model. Hazard ratio and its 95% CI for all patients are based on a stratified Cox regression model stratified by randomization stratification factors.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_04_01_os_sub.sas 15MAY23:20:54 Output File: f_14_02_02_04_01_os_sub.rtf

Figure 33. Forest Plot of Overall Survival for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups - Key Secondary Efficacy Analysis (ITT Population)



The data cut-off date is 31JAN2023.
If the subgroups are too small (<10 events), the analyses would not be provided.
Hazard ratio and its 95% CI for subgroups are based on unstratified Cox regression model. Hazard ratio and its 95% CI for all patients are based on a stratified Cox regression model stratified by randomization stratification factors.
PFIZER CONFIDENTIAL Source: kuppis /Volumes/data/usrfiles/programming/mdv3100/mdv3100_13/csr/prod/programs/tlf/f_14_02_02_04_02_os_sub.sas 15MAY23:20:54 Output File: f_14_02_02_04_02_os_sub.rtf

Sensitivity analyses

MFS - Enzalutamide Plus Leuprolide vs Placebo Plus Leuprolide

Table 30. Summary of Sensitivity Analysis for MFS for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups (ITT Population)

MFS Follow-up (in Months)	**ENZA + LA (N = 355)**	**PBO + LA (N = 358)**
Primary - MFS Events	45 (12.7%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.424 (0.296, 0.607)	
Sensitivity 1 - MFS Events Based on Independent Central Review Assessment Including Events Regardless of Initiation of Antineoplastic Therapies	52 (14.6%)	108 (30.2%)
Median (95% CI)	NR (NR, NR)	85.1 (82.9, NR)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.435 (0.312, 0.607)	
Sensitivity 2 - MFS Events Based on Independent Central Review Assessment (eITT Population)†	45 (12.7%)	92 (25.8%)

MFS Follow-up (in Months)	ENZA + LA (N = 355)	PBO + LA (N = 358)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.424 (0.296, 0.607)	
Sensitivity 3 - MFS Events Based on Investigator's Assessments	49 (13.8%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	85.1 (82.7, NR)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.470 (0.332, 0.668)	
Sensitivity 4 - MFS Events Based on Independent Central Review Assessment to Assess the Impact of Clinical Progression	45 (12.7%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	< 0.0001	
Hazard Ratio (95% CI)	0.432 (0.302, 0.619)	

The data cut-off date is 31 Jan 2023. NR = Not Reached. † MFS event percentage for Sensitivity 2 Analysis is based on eITT population of the corresponding treatment group.

Table 31. Concordance and Discordance Between BICR and Investigator Assessment for Enzalutamide plus Leuprolide vs Placebo plus Leuprolide Groups (ITT Population)

	ENZA+LA			PBO+LA			
Measures for Discordance or Concordance	**N**	**n**	**%**	**N**	**n**	**%**	**Difference (%)**
Total Event Discrepancy Rate (b+c) / N	355	28	7.9	358	34	9.5	-1.6
Early Discrepancy Rate (a3+b) / (a+b)	49	18	36.7	92	24	26.1	10.6
Late Discrepancy Rate (a2+c) / (a2+a3+b+c)	35	17	48.6	57	33	57.9	-9.3
Overall Discrepancy Rate (a2+a3+b+c) / N	355	35	9.9	358	57	15.9	-6.0
Overall Concordance Rate (a+d)/N	355	327	92.1	358	324	90.5	1.6

The data cut-off date is 31 Jan 2023. a = a1 + a2 + a3. N= a+b+c+d representing the number of patients in the ITT population.

a1 = number of agreements on timing and occurrence of PD
a2 = number of times agreement on PD event but investigator declares PD event later than BICR
a3 = number of times agreement on PD event but investigator declares PD event earlier than BICR; PD = progressive disease. b = BICR indicates not an event, but Investigator indicates an event. c = BICR indicates an event, but Investigator indicates not an event.
d = Both BICR assessment and Investigator assessment indicate not an event.
The timing agreement of progression defined as a window of +/- 7 days.

MFS -Enzalutamide Monotherapy vs Placebo Plus Leuprolide

Table 32: Summary of Sensitivity Analysis for MFS for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups (ITT Population)

MFS Follow-up (in Months)	ENZA (N = 355)	PBO + LA (N = 358)
Primary - MFS Events	63 (17.7%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	0.0049	
Hazard Ratio (95% CI)	0.631 (0.456, 0.871)	
Sensitivity 1 - MFS Events Based on Independent Central Review Assessment Including Events Regardless of Initiation of Antineoplastic Therapies	74 (20.8%)	108 (30.2%)
Median (95% CI)	NR (NR, NR)	85.1 (82.9, NR)
P-value	0.0036	
Hazard Ratio (95% CI)	0.644 (0.478, 0.867)	
Sensitivity 2 - MFS Events Based on Independent Central Review Assessment (eITT Population)†	63 (17.8%)	92 (25.8%)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	0.0049	
Hazard Ratio (95% CI)	0.631 (0.456, 0.871)	
Sensitivity 3 - MFS Events Based on Investigator's Assessments	56 (15.8%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	85.1 (82.7, NR)
P-value	0.0006	
Hazard Ratio (95% CI)	0.561 (0.401, 0.784)	
Sensitivity 4 - MFS Events Based on Independent Central Review Assessment to Assess the Impact of Clinical Progression	65 (18.3%)	92 (25.7%)
Median (95% CI)	NR (NR, NR)	NR (85.1, NR)
P-value	0.0074	
Hazard Ratio (95% CI)	0.647 (0.470, 0.892)	

The data cut-off date is 31 Jan 2023. NR = Not Reached. † MFS event percentage for Sensitivity 2 Analysis is based on eITT population of the corresponding treatment group

Table 33. Concordance and Discordance Between BICR and Investigator Assessment for Enzalutamide Monotherapy vs Placebo plus Leuprolide Groups (ITT Population)

Measures for Discordance or Concordance	ENZA			PBO+LA			Difference (%)
	N	n	%	N	n	%	
Total Event Discrepancy Rate (b+c) / N	355	33	9.3	358	34	9.5	-0.2

Measures for Discordance or Concordance	ENZA			PBO+LA			Difference (%)
	N	n	%	N	n	%	
Early Discrepancy Rate (a3+b) / (a+b)	56	15	26.8	92	24	26.1	0.7
Late Discrepancy Rate (a2+c) / (a2+a3+b+c)	43	28	65.1	57	33	57.9	7.2
Overall Discrepancy Rate (a2+a3+b+c) / N	355	43	12.1	358	57	15.9	-3.8
Overall Concordance Rate (a+d)/N	355	322	90.7	358	324	90.5	0.2

The data cut-off date is 31 Jan 2023. a = a1 + a2 + a3. N= a+b+c+d representing the number of patients in the ITT population.
a1 = number of agreements on timing and occurrence of PD
a2 = number of times agreement on PD event but investigator declares PD event later than BICR
a3 = number of times agreement on PD event but investigator declares PD event earlier than BICR;PD = progressive disease. b = BICR indicates not an event, but Investigator indicates an event. c = BICR indicates an event, but Investigator indicates not an event.
d = Both BICR assessment and Investigator assessment indicate not an event.
The timing agreement of progression defined as a window of +/- 7 days.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34: Summary of Efficacy for trial MDV3100-13 (EMBARK)

Title: Phase 3, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men With High Risk Non-metastatic Prostate Cancer Progressing After Definitive Therapy (EMBARK)			
Study identifier	Study MDV3100-13 (EMBARK)		
Design	Phase 3, three arms, double blind (combination and control arm) randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk non-metastatic prostate cancer progressing (biochemical recurrence) after definitive therapy		
	Duration of screening phase: Duration of treatment phase: Duration of Extension phase:		Day -28 to -1 36 weeks and suspension if PSA undetectable After week 37, PSA and testosterone measured every 3 months. Radiographic imaging every 6 months
Hypothesis	Superiority		
Treatments groups	Enzalutamide + ADT		Enzalutamide 160 mg/day + leuprorelin acetate 22.5 mg/12 weeks, n=355
	Enzalutamide monotherapy		Enzalutamide 160 mg/day, n=355
	Placebo + ADT		Placebo + leuprorelin acetate 22.5 mg/12 weeks, n=358
Endpoints and definitions	Primary endpoint	Metastasis-free survival (MFS)	BICR assessed by radiographic progression per RECIST 1.1 (soft tissue disease) and radiographic progression for the appearance of 1 or more metastatic lesion (bone disease) in patients with nmCSPC
	Secondary	Time to PSA progression	Time from randomisation to the date of the first PSA value demonstrating progression, defined as the date that a ≥25% increase and an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir.
	Secondary	Time to first use of new antineoplastic therapy	Time to first use of new antineoplastic therapy after study drugs discontinuation
	Secondary	OS	Time to death due to any cause based on an interim analysis.
Database lock	31-Jan-2023 (Final analysis and OS interim analysis)		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Enza + ADT	Pbo + ADT	Enza
	Number of subject	355	358	355
	MFS median (months)	NR	NR	NR
	95% CI	(NR, NR)	(85.1, NR)	(NR, NR)
	Time to PSA progression median (months)	NR	NR	NR
	95% CI	(NR, NR)	(NR, NR)	(NR, NR)
Effect estimate per comparison	Primary endpoint MFS	Comparison groups	Enza + ADT vs ADT	
		HR	0.424	
		(95% CI)	(0.296, 0.607)	
		P-value	<0.0001	
	Primary endpoint MFS	Comparison groups	Enza vs ADT	
		HR	0.631	
		(95% CI)	(0.456, 0.871)	
		P-value	P=0049	
	Secondary endpoint: Time to PSA progression	Comparison groups	Enza + ADT vs ADT	
		HR	0.068	
		(95% CI)	(0.033, 0.141)	
		P-value	P < 0.0001	
	Secondary endpoint: Time to PSA progression	Comparison groups	Enza vs ADT	
		HR	0.331	
		(95% CI)	(0.226, 0.486)	
		P-value	P < 0.0001	
Notes	OS IA at 130 (48%) events of 271 required for FA. Median OS NR in any group. HR=0.589 (95% CI: 0.382, 0.908), P=0.0153 for enza + ADT vs ADT. Enza vs ADT not formally tested, HR=0.782 (95% CI: 0.523, 1.170).			

Efficacy in Special Populations

No additional data regarding efficacy in special populations are included in this submission.

2.4.3. Discussion on clinical efficacy

Enzalutamide is currently approved for metastatic HSPC, non-metastatic CRPC and metastatic CRPC, after docetaxel or asymptomatic or mildly symptomatic patients in whom chemotherapy is not yet clinically indicated (see SmPC section 4.1). Within the current procedure, the MAH is seeking authorization for treatment of patients with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy.

Design and conduct of clinical studies

This assessment is based on the results from Study MDV3100-13 (EMBARK), a phase 3, randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk non-metastatic prostate cancer progressing (biochemical recurrence) after definitive therapy.

The patients enrolled in this study represent a population with a high risk of developing metastases defined, in this case, as prostate-specific antigen doubling time (PSADT) ≤9 months and screening PSA of ≥1 ng/mL for patients with prior radical prostatectomy or, at least, 2 ng/mL above the nadir for patients who had prior primary radiotherapy only. This means that only PSA values were taken into account to select this high-risk population whereas the *EAU Guidelines on Prostate Cancer 2023* contemplates also International Society of Urological Pathology (ISUP) grade and interval to biochemical failure. Despite the fact that patients who present a BCR with a PSADT ≤9 months are indeed considered as being at a high risk of developing metastases, the need of immediate treatment in this setting remains controversial.

The target indication is focused on patients initially treated with curative intent who are unsuitable for salvage radiotherapy based on standard guidelines, at the investigator's discretion, in line with the exclusion criteria. It is therefore, expected that the patient candidates would be those for whom immediate systemic treatment is deemed appropriate and were to receive ADT.

The study was double blind for the main comparison (enzalutamide + ADT vs. ADT) but open-label for enzalutamide monotherapy due to the impossibility to mask the LHRH analogue injections.

Patients received treatment until PSA evaluation at Week 36 by central laboratory. If PSA values were undetectable (<0.2 ng/mL) at this time point, treatment was suspended and it could be later resumed if subsequent central lab PSA results increased to ≥2.0 ng/mL for participants with prior prostatectomy or ≥5.0 ng/mL for participants without prostatectomy. Intermittent ADT has been established as a treatment option that could mitigate ADT common side effects, based on the results from different studies and meta-analyses but the impact on survival remains uncertain (Dong Z et al, Aging Male. 2015). A similar approach has been used in the EMBARK study, allowing patients to stop treatment. This strategy can be endorsed, as a threshold for rising PSA values was implemented and treatment could be reinitiated if needed.

The primary study objective was to evaluate the efficacy of the combination of enzalutamide plus leuprorelin in comparison to leuprorelin monotherapy while a secondary objective was to assess the same for enzalutamide monotherapy compared to leuprorelin. Metastases-free survival (MFS) was chosen as the primary endpoint. The relevance of this endpoint, in terms of showing a clinical benefit in a non-metastatic setting, was previously discussed during the assessment of the PROSPER study (EMEA/H/C/002639/II/0039/G) in which a group of experts were also consulted. It is assumed that a delay in the development of metastasis entails a direct benefit since symptomatic lesions carry a high disease burden on patients. However, it is also acknowledged that some metastatic disease forms can present a slow progress and remain asymptomatic for a long time. Of note, in the previously mentioned PROSPER study, similarly to what happened with the study of apalutamide in nmCRPC (SPARTAN study), the benefit in MFS was translated into an OS advantage. Time to PSA progression, time to first use of new antineoplastic therapy and OS are (key) secondary endpoints included also in the multiplicity adjustment scheme.

Randomization was stratified by screening PSA value (≤10 ng/mL vs >10 ng/mL), PSA doubling time (≤3 months vs > 3 to ≤9 months) and prior hormonal therapy (yes vs no). All these three factors are considered to have prognostic value in this setting and are agreed.

The operating characteristics for the calculation of the sample size are clear and the assumptions for the calculations are endorsed. Based on the SAP (version 3.1, dated 10-Jan-2023), if the test for the primary endpoint (MFS in the combination treatment group) was significant at the full 2-sided alpha level of 0.05, the key secondary endpoints for the combination group were to be tested at a 2-sided alpha of 0.02 utilizing a hierarchical approach to preserve the type I error rate. The remaining 0.03 alpha was to be allocated to compare MFS as well as other key secondary endpoints for enzalutamide monotherapy vs placebo plus leuprolide. The alpha for OS was dependent upon the remaining alpha from earlier tests of the other endpoints from both the combination and monotherapy treatment comparisons and the

Haybittle-Peto adjustment for the interim OS analysis. The proposal for the OS interim analysis and their efficacy boundaries shows that the final analysis is to be performed using a 0.05 level of significance as usual. Therefore, there are no concerns to the multiple adjustment.

Up to the data cut-off (31-Jan-2023), four protocol amendments were implemented. Amendment 4 (29-Oct-2021) included some relevant changes to the primary endpoint (the primary endpoint was re-powered and the IA was removed). According to the MAH, these changes were based on external data, mainly the results from the PROSPER and SPARTAN studies of enzalutamide and apalutamide, respectively, in nmCRPC, in addition to a subpopulation from the STAMPEDE platform study similar to the one enrolled in EMBARK study. In these studies, the reported HR for MFS (HR 0.29 [95% CI: 0.24, 0.35] and HR 0.28 [95% CI: 0.23, 0.35] for PROSPER and SPARTAN, respectively, and HR 0.53 [95% CI: 0.44, 0.64] for STAMPEDE) were lower than the original target HR for MFS (0.65) in the EMBARK study. Therefore, the primary endpoint was repowered, aiming at a lower HR of 0.58, and the MFS IA was removed. These studies were published before amendment 4 was issued and, overall, the MAH's rationale can be followed and there were no major concerns with regard to the conduct of the study.

Patients with at least one major protocol deviation were 51 out 1068, with a slight imbalance towards a higher percentage in the enzalutamide monotherapy: 23 out 355 (6.5%) in the enzalutamide monotherapy vs. 11 out 358 (3.1%) in the placebo arm. The most frequently reported protocol deviation category was "IP Compliance" (4.5% vs 1.7%). This trend was similar in the enzalutamide plus leuprolide arm (4.5% vs 2.5%).

Efficacy data and additional analyses

A total of 1813 participants were screened and 1068 patients were randomized to the enzalutamide plus leuprolide group (n=355), placebo plus leuprolide group (n=358), or enzalutamide monotherapy group (n=355).

The demographic and baseline characteristics were well balanced between the three treatment groups. The overall median age at randomisation was 69 years (range: 49.0 – 93.0). 23.4% of randomized patients were ≥75 years of age, which represents the usual prostate cancer population Most patients in the total population were Caucasian (83.2%), 7.3% were Asian, and 4.4% were Black. Slight differences between treatment arms were identified, especially for patients with PSADT >3 - ≤6 months vs >6 - ≤9 months, with a slightly higher rate of poorer prognostic patients in the enzalutamide + ADT group. As previously stated, high risk population to be included in this trial was only defined by PSADT/PSA at screening but there are other poor prognosis risk factors that are usually considered to decide the treatment management in this BCR setting. Baseline median total Gleason score was 7 in all groups with most of the participants being classified in the medium (5-7) Gleason score group and only one third of the patients in the high (8-10) Gleason score group. This is highlighted because patients with a high Gleason score would definitely be considered as high risk but it is not that clear for medium Gleason score, as the majority of participants from the EMBARK study. Nevertheless, this corresponds to the design of the trial, therefore the target population would be the one that meets the inclusion criteria from the EMBARK study. This should be considered in the context of emerging data that suggest cross resistance between enzalutamide and abiraterone, with the risk of restricting successful subsequent treatment options in the metastatic setting[35]. At this stage, this uncertainty remains due to the low number of patients from the enzalutamide + ADT (16.3%) arm and enzalutamide monotherapy (23.7%) group that have received subsequent treatment. As expected, some of these patients received docetaxel in a later disease stage but a non-negligible number of patients, especially from the ADT group, received leuprorelin treatment as subsequent therapy.

Regarding the protocol established treatment suspension in patients who had undetectable PSA at week 36, in the safety population (n=1061), 321 (90.9%) patients in the enzalutamide plus ADT group, 240 (67.8%) patients in the placebo plus ADT group and 304 (85.9%) patients in the enzalutamide monotherapy group suspended treatment for this reason. Most of these patients required reinitiating treatment, with a lower relative percentage in the enzalutamide plus ADT group (75.1% enzalutamide + ADT arm vs 84.6% placebo + ADT arm vs 88.2% in the enzalutamide monotherapy treatment group). There were 80 (22.7%) patients in the combination arm, 37 (10.5%) in the ADT group and 34 (9.6%) patients in the enzalutamide monotherapy arm that suspended treatment and never reinitiated.

An improvement in MFS in the enzalutamide plus ADT arm compared to the placebo plus leuprolide treatment group was shown, with a HR point estimate of 0.424 (95% CI: 0.296, 0.607; 2-sided stratified log-rank test P <0.0001). Median MFS was not reached in any of these two treatment arms. Median follow-up was of around 61 months in both treatment arms. Of note, at the time of analysis the number of censored patients was high, 310 (87.3%) in the enzalutamide + ADT arm and 266 (74.3%) in the ADT arm. Most patients were censored due to not metastatic disease or death but 36 (10.1%) patients in the enzalutamide + ADT arm and 67 (18.7%) in the ADT treatment arm were censored due to initiation of subsequent antineoplastic therapy. This shows an imbalance favouring the combination arm which, in line with EMA guidance, suggests the possibility of informative censoring. However, the sensitivity analysis conducted confirmed consistent results (see below). Subgroup analyses were overall consistent with the primary analysis and no relevant differences were identified.

Key secondary endpoint results also showed a benefit, in terms of MFS, for enzalutamide monotherapy in comparison with ADT. Estimated HR was 0.631 (95% CI: 0.456, 0.871; 2-sided stratified log-rank test P = 0.0049) and median MFS was not reached for the enzalutamide monotherapy group. A total of 292 (82.3%) patients from the enzalutamide arm and 266 (74.3%) from the leuprolide arm were censored at the time of this analysis, most because no event occurred, as expected. Again, an imbalance favouring enzalutamide arm was observed regarding censored patients due to initiation of antineoplastic therapy.

All the five sensitivity analyses performed for the primary endpoint of MFS support the robustness of the outcomes since all of them were met.

Other secondary endpoints included in the multiplicity adjustment scheme were time to PSA progression, time to first use of new antineoplastic therapy and OS, all favouring the combination arm and enzalutamide monotherapy over ADT.

The pre-specified efficacy boundary (P ≤0.0001) was not crossed at this interim OS analysis. Therefore, OS for the monotherapy arm was not formally tested. There was a trend in favour of the enzalutamide monotherapy compared with ADT (HR = 0.782 [95% CI: 0.523, 1.170], although the benefit is not as clear as for the combination arm. Subgroup analyses for OS were generally consistent with the primary analysis although the limited number of events preclude any conclusion. Despite the low number of OS data, a detrimental effect in survival appears unlikely for enzalutamide + ADT over ADT alone and for enzalutamide monotherapy compared with ADT. Considering the immaturity of data, the MAH is recommended to provide the final results of the EMBARK study including OS data when available (REC).

All the other secondary time-to-event endpoints clearly favoured the combination of enzalutamide + ADT. A positive trend was also identified for enzalutamide monotherapy compared to ADT, although the benefit was not as remarkable as for the combination, as previously observed for the other endpoints.

A higher proportion of patients from the enzalutamide + ADT group remained treatment free 2 years after suspension of treatment: 34.6% enzalutamide+ADT vs 27.1% from the ADT group. Interestingly, a quite lower proportion (14.1%) was observed in the enzalutamide monotherapy arm, and the same trend was followed for participants with undetectable PSA at 2 years after suspension. As expected, testosterone

levels stayed constant during all treatment for patients in the enzalutamide monotherapy group, which can be also seen for the safety profile of this treatment option.

In line with the design of the EMBARK study, a recommendation is included in section 4.2 to suspend treatment with enzalutamide (+ LHRH analogue) if PSA is undetectable (<0.2 ng/mL) at week 36, as well as the possibility to re-initiate treatment if PSA increases to ≥ 2.0 ng/mL for patients who had prior radical prostatectomy or ≥5.0 ng/mL for patients who had prior primary radiation therapy. Of note, the majority of patients in EMBARK Study that has suspended treatment required treatment re-initiation and although treatment interruption could be an option to attenuate toxicity, it is not possible to ascertain whether this strategy may have an impact on the efficacy as compared to a continuous administration. However, a clear benefit has been shown for enzalutamide + leuprolide regardless of a high number of patients having stopped treatment at Week 37 (even though most of them reinitiated) therefore no conclusions diverting from that are possible based on the available information. In any case, the criteria established for stopping and reintroducing treatment in the study protocol seemed strict enough and are considered acceptable to support this option. PFS2 was included as an exploratory endpoint. A total of 36 (10.1%) patients in the enzalutamide plus leuprolide group, 63 (17.6%) patients in the placebo plus leuprolide group, and 48 (13.5%) patients in the enzalutamide monotherapy group experienced first investigator-determined disease progression. The HR point estimate was 0.521 (95% CI: 0.345, 0.786) for the enzalutamide + ADT comparison and 0.739 (95% CI: 0.507, 1.077) for the monotherapy, compared to ADT. Even when the number of events included in this analysis is low, these results support the exclusion of any detrimental long-term effect of enzalutamide in this setting.

Time to deterioration in FACT-P total score was also analysed and no relevant differences were identified between treatment groups. Additional PRO analyses in the Embark study support the use of both enzalutamide in combination with ADT and as monotherapy in this setting.

Wording of the indication

Initially the claimed indication was "*for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy"*, followed by a statement in section 4.2 recommending the administration of enzalutamide with an LHRH analogue. During the procedure, the MAH proposed to amend Section 4.2 of the SmPC to reflect the use of enzalutamide also in monotherapy, without an LHRH analogue, as a treatment for nmHSPC with high-risk BCR. MFS data supporting the use of enzulatamide in monotherapy for the proposed patient population were provided as secondary objective in the EMBARK study. Efficacy MFS endpoint and all the remaining secondary endpoints clearly showed a benefit with the use of enzalutamide in monotherapy except for the OS. Although a trend in favour of enzalutamide as monotherapy is observed (the HR point estimate for the OS was <1) the CI was quite wide (HR = 0.782 [95% CI: 0.523, 1.170]; nominal P = 0.2304) when comparing enzalutamide + ADT vs ADT. Based on the study results, there is no indication of detrimental effect in survival. Nevertheless, the OS data are immature and the MAH is recommended to provide updated OS data from study EMBARK when available. Following assessment of the data submitted, the initial indication has been reviewed and the accepted indication is:

Xtandi is indicated:

"*as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy (see section 5.1).*"

Additionally, it was considered relevant to reflect in the SmPC that the monotherapy is not an equivalent treatment option compared to the combination with ADT in patients with high risk BCR nmHSPC, and that the combination with ADT is considered the preferred treatment option, except for cases in which the addition of ADT may result in unacceptable toxicity or risk (see SmPC 4.4).

2.4.4. Conclusions on the clinical efficacy

Based on the efficacy results of study EMBARK, enzalutamide in combination with leuprorelin has shown a clinically relevant benefit over leuprorelin alone in patients with high risk nmCRPC. The benefit has been also shown for enzalutamide as monotherapy compared with leuprorelin alone, although at lower extent.

Uncertainties remain with regard to the maturity of the OS data. The MAH is recommended to provide the final OS analysis from Study MDV3100-13 (EMBARK) when available (REC).

2.5. Clinical safety

Introduction

The integrated summary of safety of this submission includes safety data from 8 clinical studies of enzalutamide in patients with nonmetastatic and metastatic HSPC and nonmetastatic and metastatic CRPC to support the safety profile from the EMBARK study (MDV3100-13). In addition to the EMBARK study in patients with nmCSPC, the integrated safety data include:

- One randomized, placebo-controlled, phase 3 study in patients with nmCRPC (PROSPER [MDV3100-14])
- One randomized, placebo-controlled, phase 3 study in patients with mHSPC (ARCHES [9785-CL-0335])
- One randomized, placebo-controlled, phase 3 study in patients with mCRPC previously treated with docetaxel-based chemotherapy (AFFIRM [CRPC2])
- Two randomized, placebo-controlled, phase 3 studies in chemotherapy-naïve patients with mCRPC (PREVAIL [MDV3100-03] and Asian PREVAIL [9785-CL-0232])
- Two randomized, bicalutamide-controlled phase 2 studies in patients with mCRPC (TERRAIN [9785-CL-0222]) and with nonmetastatic or metastatic CRPC (STRIVE [MDV3100-09])

With the exception of patients in the enzalutamide monotherapy arm in the EMBARK study, all other patients in these studies received ADT (medical or surgical) to maintain castration levels of testosterone. Together these studies included 5110 patients treated with enzalutamide 160 mg/day (± ADT) that make up the integrated safety population and 2829 patients treated with placebo plus ADT.

Table 35. Enzalutamide studies included in the safety pool

Study Identifier/ Data Cutoff	Phase and Blinding	Study Population	No. Treated Patients†	Study Drugs and Dose	Primary Endpoints	Safety Data Collected
EMBARK (MDV3100-13)/ 31 Jan 2023	Phase 3 randomized DB and OL arms in parallel	Patients with high-risk nonmetastatic prostate cancer progressing after either radical prostatectomy or radiotherapy (nmCSPC)	1061 patients in total; 353 enzalutamide + ADT (DB) 354 placebo + ADT (DB) 354 enzalutamide monotherapy (OL)	Enzalutamide 160 mg/day + Leuprolide (DB), Placebo + Leuprolide (DB), Enzalutamide 160 mg/day (OL)	MFS‡	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
PROSPER (MDV3100-14)/ 15 Oct 2019	Phase 3 DB period followed by OL extension	Patients with nmCRPC	930 enzalutamide, 465 placebo (87 crossover)	Enzalutamide 160 mg/day, Placebo	MFS§	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
ARCHES (9785-CL-0335)/ 28 May 2021	Phase 3 DB period followed by OL extension	Patients with mCSPC	572 enzalutamide, 574 placebo (180 crossover)	Enzalutamide 160 mg/day, Placebo	rPFS¶	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
AFFIRM (CRPC2)/ 20 Feb 2018	Phase 3 DB period followed by OL extension	Patients with progressive CRPC who have been previously treated with docetaxel-based chemotherapy	800 enzalutamide, 399 placebo (50 crossover)	Enzalutamide 160 mg/day, Placebo	OS	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
PREVAIL (MDV3100-03)/ 21 Mar 2019	Phase 3 DB period followed by OL extension	Patients with asymptomatic or mildly symptomatic progressive mCRPC	871 enzalutamide, 844 placebo (234 crossover)	Enzalutamide 160 mg/day, Placebo	OS, rPFS	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
Asian PREVAIL (9785-CL-0232) (excl. site 105)/ 04 Nov 2020	Phase 3 DB period followed by OL extension	Chemotherapy-naive patients with progressive, metastatic prostate cancer who failed ADT	202 enzalutamide, 193 placebo (51 crossover)	Enzalutamide 160 mg/day, Placebo	TTPP††	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
TERRAIN (9785-CL-0222)/ 17 Feb 2018	Phase 2 DB period followed by OL extension	Patients with metastatic prostate cancer who have progressed while on LHRH agonist/antagonist or after receiving a bilateral orchiectomy	183 enzalutamide, 189 bicalutamide (9 crossover)	Enzalutamide 160 mg/day, Bicalutamide 50 mg/day	PFS‡‡	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death
STRIVE (MDV3100-09)/ 30 May 2018	Phase 2 DB period followed by OL extension	Patients with recurrent prostate cancer who have serologic and/or radiographic disease progression despite primary ADT	197 enzalutamide, 198 bicalutamide (37 crossover)	Enzalutamide 160 mg/day Bicalutamide 50 mg/day	PFS§§	Drug exposure, AEs, laboratory assessment, ECGs, vital signs, death

ADT: androgen deprivation therapy; AE: adverse event; BICR: blinded independent central review; CRPC: castration-resistant prostate cancer; DB: double-blind; ECG: electrocardiogram; excl: excluding; ISS: Integrated Summary of Safety; LHRH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; mCSPC: metastatic castration-sensitive prostate cancer; MFS: metastasis-free survival; nmCRPC: nonmetastatic castration-resistant prostate cancer; nmCSPC: nonmetastatic castration-sensitive prostate cancer; OL: open-label; OS: overall survival; PCWG2: Prostate Cancer Clinical Trials Working Group 2; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival; SAP: statistical analysis plan; SCS: Summary of Clinical Safety; TTPP: time to PSA progression.

† Crossover refers to the number of patients treated with enzalutamide in open-label phase after receiving placebo/bicalutamide in double-blind phase.

‡ MFS was defined as the time in months between randomization and the earliest objective evidence of radiographic progression as determined by BICR, or death due to any cause without evidence of radiographic progression, whichever occurred first. Primary endpoint was MFS between enzalutamide plus leuprolide and placebo plus leuprolide.

§ MFS was defined as the time from randomization to radiographic progression at any time or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first.

¶ rPFS was defined as objective evidence of radiographic disease progression based on the assessments by the independent radiographic review at any time or death from any cause within 24 weeks from study drug discontinuation, whichever occurred first.

†† TTPP was defined as the time from randomization to the date of the first confirmed observation of PSA progression.

‡‡ PFS was defined as the time from randomization to objective evidence of radiographic disease progression based on the assessments by the independent radiographic review, skeletal-related event, initiation of new antineoplastic therapy or death by any cause.

§§ PFS was defined as the time from randomization to the earliest objective evidence of radiographic progression, PSA progression by PCWG2 criteria or death due to any cause.

Table 36. Description of integrated safety groups

Study or Pool	Studies Included	Treatment Arms/ Study Period	Treatment Groups Presented
EMBARK (nmCSPC)	EMBARK	DB and OL arms	Enzalutamide + ADT (DB) (n=353) Placebo + ADT (DB) (n=354) Enzalutamide monotherapy (OL) (n=354)
nmPC phase 3 studies	EMBARK PROSPER	Enzalutamide + ADT and Placebo + ADT arms for EMBARK; DB period for PROSPER	Enzalutamide + ADT (n=1283) Placebo + ADT (n=819)
Phase 3 studies	EMBARK PROSPER ARCHES AFFIRM PREVAIL Asian PREVAIL	Enzalutamide + ADT and Placebo + ADT arms for EMBARK; DB period for other studies	Enzalutamide + ADT (n=3728) Placebo + ADT (n=2829)
Total enzalutamide (phase 2 and 3 studies)	EMBARK PROSPER ARCHES AFFIRM PREVAIL Asian PREVAIL TERRAIN STRIVE	Enzalutamide + ADT and Enzalutamide monotherapy arms for EMBARK; Enzalutamide + ADT in DB and/or OL period for other studies	Enzalutamide ± ADT (n=5110)

ADT: androgen deprivation therapy; DB: double-blind; ISS: Integrated Summary of Safety; nmCSPC: nonmetastatic castration-sensitive prostate cancer; nmPC: nonmetastatic prostate cancer; OL: open-label; SCS: Summary of Clinical Safety.

Patient exposure

Table 37. Extent of exposure (Safety Groups)

Category	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Total treatment duration, years	1525.867	1411.261	1562.804	6933.227	3414.768	11871.248
Total treatment duration, months§	18310.407	16935.129	18753.643	83198.722	40977.211	142454.97
Treatment duration, months§						
Mean (SD)	51.87 (26.25)	47.84 (24.74)	52.98 (24.06)	22.32 (17.63)	14.48 (17.12)	27.88 (22.16)
Median	60.65	55.64	60.39	19.30	8.38	22.10
Minimum, Maximum	0.1, 90.4	0.7, 94.1	0.4, 95.0	0.0, 90.4	0.1, 94.1	0.0, 95.0
Treatment duration category (months), n (%)						
< 3	10 (2.8)	6 (1.7)	6 (1.7)	279 (7.5)	537 (19.0)	386 (7.6)
≥ 3 to < 6	9 (2.5)	8 (2.3)	11 (3.1)	340 (9.1)	623 (22.0)	478 (9.4)
≥ 6 to < 12	49 (13.9)	40 (11.3)	24 (6.8)	625 (16.8)	541 (19.1)	808 (15.8)
≥ 12 to < 24	7 (2.0)	29 (8.2)	20 (5.6)	1073 (28.8)	720 (25.5)	1043 (20.4)
≥ 24 to < 36	19 (5.4)	36 (10.2)	25 (7.1)	791 (21.2)	147 (5.2)	702 (13.7)
≥ 36 to < 48	17 (4.8)	33 (9.3)	34 (9.6)	299 (8.0)	58 (2.1)	622 (12.2)
≥ 48 to < 60	57 (16.1)	59 (16.7)	55 (15.5)	116 (3.1)	60 (2.1)	504 (9.9)
≥ 60	185 (52.4)	143 (40.4)	179 (50.6)	205 (5.5)	143 (5.1)	567 (11.1)
Number of dose interruptions, n (%)						
0	291 (82.4)	298 (84.2)	283 (79.9)	3146 (84.4)	2511 (88.8)	4276 (83.7)
1	41 (11.6)	43 (12.1)	55 (15.5)	433 (11.6)	261 (9.2)	617 (12.1)
2	20 (5.7)	10 (2.8)	7 (2.0)	93 (2.5)	44 (1.6)	138 (2.7)
3	0	3 (0.8)	7 (2.0)	33 (0.9)	10 (0.4)	48 (0.9)
4	1 (0.3)	0	2 (0.6)	13 (0.3)	2 (0.1)	21 (0.4)
5	0	0	0	1 (0.0)	1 (0.0)	1 (0.0)
6	0	0	0	5 (0.1)	0	5 (0.1)

>6	0	0	0	4 (0.1)	0	4 (0.1)
Reason for dose interruption¶, n (%)						
Adverse event	54 (15.3)	42 (11.9)	65 (18.4)	534 (14.3)	271 (9.6)	760 (14.9)
Other	14 (4.0)	19 (5.4)	10 (2.8)	77 (2.1)	61 (2.2)	119 (2.3)
Number of dose reductions, n (%)						
0	327 (92.6)	336 (94.9)	294 (83.1)	3497 (93.8)	2753 (97.3)	4724 (92.4)
1	17 (4.8)	8 (2.3)	32 (9.0)	141 (3.8)	50 (1.8)	232 (4.5)
2	4 (1.1)	6 (1.7)	16 (4.5)	51 (1.4)	13 (0.5)	96 (1.9)
3	4 (1.1)	2 (0.6)	7 (2.0)	21 (0.6)	7 (0.2)	32 (0.6)
4	1 (0.3)	1 (0.3)	3 (0.8)	9 (0.2)	3 (0.1)	14 (0.3)
5	0	0	2 (0.6)	6 (0.2)	1 (0.0)	9 (0.2)
6	0	0	0	1 (0.0)	0	1 (0.0)
>6	0	1 (0.3)	0	2 (0.1)	2 (0.1)	2 (0.0)
Reason for dose reduction¶, n (%)						
Adverse event	25 (7.1)	15 (4.2)	53 (15.0)	210 (5.6)	67 (2.4)	345 (6.8)
Other	3 (0.8)	3 (0.8)	8 (2.3)	40 (1.1)	13 (0.5)	72 (1.4)
Number of dose modifications (includes interruptions, reductions and treatment suspension due to undetectable PSA), n (%)						
0	23 (6.5)	89 (25.1)	28 (7.9)	2821 (75.7)	2287 (80.8)	3655 (71.5)
1	263 (74.5)	219 (61.9)	238 (67.2)	608 (16.3)	420 (14.8)	968 (18.9)
2	38 (10.8)	31 (8.8)	51 (14.4)	155 (4.2)	81 (2.9)	269 (5.3)
3	17 (4.8)	6 (1.7)	11 (3.1)	71 (1.9)	19 (0.7)	104 (2.0)
4	7 (2.0)	4 (1.1)	11 (3.1)	34 (0.9)	10 (0.4)	52 (1.0)
5	2 (0.6)	2 (0.6)	9 (2.5)	11 (0.3)	5 (0.2)	24 (0.5)
6	2 (0.6)	2 (0.6)	2 (0.6)	9 (0.2)	5 (0.2)	12 (0.2)
>6	1 (0.3)	1 (0.3)	4 (1.1)	19 (0.5)	2 (0.1)	26 (0.5)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. By definition for EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population). All 1061 treated patients in the EMBARK study received at least 1 dose of enzalutamide or placebo, the same as the other pooled studies.

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Treatment duration in the respective phase was defined as [(the date of last dosing)-(the date of first dosing) +1] /30.4375 for patients who discontinued treatment and [(the data cutoff date)-(the date of first dosing) +1] /30.4375 for patients still on treatment by the cutoff date.

¶ Patients with multiple reasons for dose interruptions/reductions were counted only once for each reason.

Per the protocol, treatment was to be suspended in the EMBARK study in patients who had undetectable PSA at week 36. In the safety population, 321/353 (90.9%) patients in the enzalutamide plus ADT group, 240/354 (67.8%) patients in the placebo plus ADT group and 304/354 (85.9%) patients in the enzalutamide monotherapy group had treatment suspended per protocol.

Because study treatment was suspended in the EMBARK study for patients who had undetectable PSA at week 36, a modified treatment duration was calculated excluding the period of treatment suspension.

Table 38. Enzalutamide / placebo extent of exposure and treatment compliance (EMBARK study, Safety Population)

	ENZA + LA (N=353)	PBO + LA (N=354)	ENZA (N=354)	Total (N=1061)
Treatment Duration (Months) [1]				
n	353	354	354	1061
Mean (SD)	51.9 (26.25)	47.8 (24.74)	53.0 (24.06)	50.9 (25.11)
Median	60.6	55.6	60.4	59.0
Min, Max	0.1, 90.4	0.7, 94.1	0.4, 95.0	0.1, 95.0
Treatment Duration Category (Months)				
<6	19 (5.4%)	14 (4.0%)	17 (4.8%)	50 (4.7%)
6 to <12	49 (13.9%)	40 (11.3%)	24 (6.8%)	113 (10.7%)
12 to <24	7 (2.0%)	29 (8.2%)	20 (5.6%)	56 (5.3%)
24 to <36	19 (5.4%)	36 (10.2%)	25 (7.1%)	80 (7.5%)
36 to <48	17 (4.8%)	33 (9.3%)	34 (9.6%)	84 (7.9%)
48 to <60	57 (16.1%)	59 (16.7%)	55 (15.5%)	171 (16.1%)
60 to <72	102 (28.9%)	81 (22.9%)	99 (28.0%)	282 (26.6%)
>=72	83 (23.5%)	62 (17.5%)	80 (22.6%)	225 (21.2%)
Treatment Suspension Duration (Months) [2]				
n	321	240	304	865
Mean (SD)	29.9 (20.61)	24.4 (18.68)	18.0 (18.14)	24.2 (19.88)
Median	20.2	16.8	11.1	16.8
Min, Max	5.7, 87.9	3.4, 83.0	2.3, 84.9	2.3, 87.9
Treatment Suspension Duration Category (Months)				
<6	2 (0.6%)	5 (2.1%)	73 (24.0%)	80 (9.2%)
6 to <12	70 (21.8%)	66 (27.5%)	108 (35.5%)	244 (28.2%)
12 to <24	108 (33.6%)	92 (38.3%)	61 (20.1%)	261 (30.2%)
24 to <36	34 (10.6%)	31 (12.9%)	20 (6.6%)	85 (9.8%)
36 to <48	27 (8.4%)	5 (2.1%)	7 (2.3%)	39 (4.5%)
48 to <60	41 (12.8%)	24 (10.0%)	20 (6.6%)	85 (9.8%)
60 to <72	27 (8.4%)	9 (3.8%)	7 (2.3%)	43 (5.0%)
>=72	12 (3.7%)	8 (3.3%)	8 (2.6%)	28 (3.2%)
Modified Treatment Duration (Months) [3]				
n	353	354	354	1061
Mean (SD)	32.5 (22.31)	35.2 (21.46)	41.2 (22.49)	36.3 (22.37)
Median	32.4	35.4	45.9	38.7
Min, Max	0.1, 83.4	0.7, 85.7	0.4, 88.9	0.1, 88.9
Modified Treatment Duration Category (Months)				
<6	19 (5.4%)	15 (4.2%)	17 (4.8%)	51 (4.8%)
6 to <12	97 (27.5%)	61 (17.2%)	49 (13.8%)	207 (19.5%)
12 to <24	35 (9.9%)	52 (14.7%)	29 (8.2%)	116 (10.9%)
24 to <36	36 (10.2%)	52 (14.7%)	38 (10.7%)	126 (11.9%)
36 to <48	66 (18.7%)	71 (20.1%)	63 (17.8%)	200 (18.9%)
48 to <60	52 (14.7%)	54 (15.3%)	79 (22.3%)	185 (17.4%)
60 to <72	38 (10.8%)	30 (8.5%)	54 (15.3%)	122 (11.5%)
>=72	10 (2.8%)	19 (5.4%)	25 (7.1%)	54 (5.1%)
Duration of Treatment after Reinitiation (Months) [4]				
n	241	203	270	714
Mean (SD)	34.0 (17.78)	32.0 (16.63)	39.0 (18.14)	35.3 (17.82)
Median	35.5	33.1	40.4	36.8
Min, Max	0.3, 70.8	0.0, 69.5	0.3, 77.6	0.0, 77.6

Duration of Treatment after Reinitiation Category (Months)				
<6	21 (8.7%)	17 (8.4%)	13 (4.8%)	51 (7.1%)
6 to <12	15 (6.2%)	15 (7.4%)	18 (6.7%)	48 (6.7%)
12 to <24	34 (14.1%)	30 (14.8%)	30 (11.1%)	94 (13.2%)
24 to <36	55 (22.8%)	54 (26.6%)	40 (14.8%)	149 (20.9%)
36 to <48	52 (21.6%)	56 (27.6%)	76 (28.1%)	184 (25.8%)
48 to <60	50 (20.7%)	19 (9.4%)	62 (23.0%)	131 (18.3%)
60 to <72	14 (5.8%)	12 (5.9%)	27 (10.0%)	53 (7.4%)
>=72	0 (0.0%)	0 (0.0%)	4 (1.5%)	4 (0.6%)
Total Number of Capsules Taken [5]				
n	352	354	354	1060
Mean (SD)	3694.9 (2594.64)	4024.0 (2492.73)	4604.3 (2623.59)	4108.5 (2595.85)
Median	3623.0	4067.0	5089.0	4257.5
Min, Max	0.0, 10080.0	97.0, 10515.0	40.0, 10312.0	0.0, 10515.0
Unknown	1	0	0	1
Cumulative Dose (mg) [6]				
n	352	354	354	1060
Mean (SD)	147794.3 (103785.52)	160959.1 (99709.22)	184173.0 (104943.68)	164340.0 (103833.87)
Median	144920.0	162680.0	203560.0	170300.0
Min, Max	0.0, 403200.0	3880.0, 420600.0	1600.0, 412480.0	0.0, 420600.0
Unknown	1	0	0	1
Average Daily Dose (mg) [7]				
n	352	354	354	1060
Mean (SD)	147.4 (32.17)	149.6 (18.83)	145.6 (21.52)	147.5 (24.86)
Median	154.7	155.5	154.1	154.7
Min, Max	0.0, 507.7	20.5, 238.1	27.1, 177.7	0.0, 507.7
Unknown	1	0	0	1
Overall Compliance Rate [8]				
n	352	354	354	1060
Mean (SD)	103.9 (49.42)	100.3 (14.85)	100.3 (8.63)	101.5 (30.18)
Median	100.0	99.7	100.1	100.0
Min, Max	0.0, 797.9	42.3, 325.0	35.8, 149.4	0.0, 797.9
Unknown	1	0	0	1
Category of Overall Compliance Rate [8]				
<20%	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
>=20% to <40%	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (<0.1%)
>=40% to <60%	3 (0.8%)	3 (0.8%)	1 (0.3%)	7 (0.7%)
>=60% to <80%	5 (1.4%)	3 (0.8%)	5 (1.4%)	13 (1.2%)
>=80% to 100%	168 (47.6%)	197 (55.6%)	167 (47.2%)	532 (50.1%)
>100% to <105%	116 (32.9%)	113 (31.9%)	138 (39.0%)	367 (34.6%)
>=105%	58 (16.4%)	38 (10.7%)	42 (11.9%)	138 (13.0%)
Unknown	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)

The data cutoff date is 31JAN2023.
[1]: (Last dose date of study drug - First dose date of study drug + 1)/30.4375.
[2]: Last date of suspension without drug (i.e., First dose after suspension - 1 or Date of data cutoff, whichever occurs first) - First date of suspension + 1.
[3]: Treatment duration - Treatment suspension duration + 1 for patients who suspended treatment and Reinitiated. Tre atment duration otherwise.
[4]: Date of last dose of study drug - First dose after suspension + 1
[5]: The number of capsules dispensed - the number of capsules returned. Capsules from bottles not returned are assu med to have not been taken.
[6]: Number of capsules taken x 40 mg.
[7]: The cumulative dose divided by the modified treatment duration.
[8]: Number of capsules taken during the study/expected number of capsules during the study multiplied by 100.

Table 39. Demographic and baseline characteristics (Safety Groups)

Baseline Characteristics	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Age group (years), n (%)						
< 65	79 (22.4)	90 (25.4)	91 (25.7)	805 (21.6)	668 (23.6)	1122 (22.0)
65 to < 75	201 (56.9)	177 (50.0)	173 (48.9)	1650 (44.3)	1239 (43.8)	2285 (44.7)
75 to < 85	72 (20.4)	82 (23.2)	84 (23.7)	1116 (29.9)	811 (28.7)	1498 (29.3)
≥ 85	1 (0.3)	5 (1.4)	6 (1.7)	157 (4.2)	111 (3.9)	205 (4.0)
Age, years						
Mean (SD)	69.1 (6.5)	69.1 (7.3)	69.1 (7.7)	70.9 (8.2)	70.5 (8.3)	70.8 (8.2)
Median (min, max)	69.0 (51, 87)	69.5 (50, 92)	69.0 (49, 93)	71.0 (41, 95)	71.0 (42, 93)	71.0 (41, 96)
Race, n (%)						
American Indian or Alaska Native	4 (1.1)	1 (0.3)	0	6 (0.2)	2 (0.1)	6 (0.1)
Asian	26 (7.4)	26 (7.3)	26 (7.3)	535 (14.4)	479 (16.9)	710 (13.9)
Black or African American	16 (4.5)	16 (4.5)	15 (4.2)	94 (2.5)	67 (2.4)	158 (3.1)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	0	6 (0.2)	3 (0.1)	8 (0.2)
White	291 (82.4)	298 (84.2)	294 (83.1)	2840 (76.2)	2094 (74.0)	3932 (76.9)
Multiple	2 (0.6)	3 (0.8)	4 (1.1)	9 (0.2)	9 (0.3)	16 (0.3)
Other	3 (0.8)	5 (1.4)	1 (0.3)	50 (1.3)	22 (0.8)	60 (1.2)
Not reported	10 (2.8)	5 (1.4)	14 (4.0)	10 (0.3)	5 (0.2)	24 (0.5)
Unknown/missing	0	0	0	178 (4.8)	148 (5.2)	196 (3.8)
Ethnicity, n (%)						
Hispanic or Latino	17 (4.8)	23 (6.5)	18 (5.1)	185 (5.0)	141 (5.0)	259 (5.1)
Not Hispanic or Latino	317 (89.8)	319 (90.1)	319 (90.1)	3155 (84.6)	2339 (82.7)	4379 (85.7)
Not reported	19 (5.4)	12 (3.4)	17 (4.8)	156 (4.2)	123 (4.3)	187 (3.7)
Unknown/Missing	0	0	0	232 (6.2)	226 (8.0)	285 (5.6)
Geographic region, n (%)						
North America	143 (40.5)	135 (38.1)	133 (37.6)	851 (22.8)	614 (21.7)	1373 (26.9)
Europe	129 (36.5)	127 (35.9)	145 (41.0)	1849 (49.6)	1367 (48.3)	2401 (47.0)
Rest of world	81 (22.9)	92 (26.0)	76 (21.5)	1028 (27.6)	848 (30.0)	1336 (26.1)
Weight, kg						
n	353	354	354	3718	2822	5095
Mean (SD)	87.38 (15.17)	87.27 (15.89)	87.54 (15.56)	83.33 (15.86)	83.15 (16.33)	84.15 (16.53)
Median (min, max)	85.00 (55.6, 157.7)	85.80 (53.7, 148.2)	85.05 (50.0, 171.8)	82.00 (42.7, 163.0)	81.30 (33.9, 167.0)	82.40 (36.4, 249.7)
BMI, kg/m^2						
n	351	351	353	2915	2419	4236
Mean (SD)	28.51 (4.22)	28.38 (4.36)	28.61 (4.71)	27.84 (4.53)	27.69 (4.59)	28.03 (4.73)
Median (min, max)	28.10 (19.9, 47.1)	28.00 (18.5, 45.9)	27.80 (17.3, 53.2)	27.29 (15.8, 51.1)	27.14 (14.9, 51.5)	27.45 (11.4, 60.5)
Baseline absolute neutrophil count (10^6/L)						
n	353	354	354	3717	2825	5040
Mean (SD)	3901.76 (1241.30)	3996.89 (1308.94)	4049.89 (1474.21)	4159.71 (1592.07)	4238.55 (1726.26)	4174.48 (1624.86)
Median (min, max)	3730.00 (1480.0, 10050.0)	3815.00 (1500.0, 9550.0)	3830.00 (1590.0, 15300.0)	3890.00 (600.0, 17540.0)	3920.00 (860.0, 26810.0)	3900.00 (160.0, 17540.0)
Baseline hemoglobin (g/L)						
n	353	354	354	3721	2826	5045
Mean (SD)	145.51 (11.80)	146.00 (11.39)	145.55 (11.70)	130.27 (15.33)	131.46 (15.08)	131.18 (15.33)
Median (min, max)	145.00 (110.0, 179.0)	146.00 (102.0, 178.0)	147.00 (113.0, 173.0)	131.00 (63.0, 179.0)	132.00 (57.0, 179.0)	132.00 (63.0, 179.0)
Baseline albumin (g/L)						
n	353	354	354	3723	2826	5050
Mean (SD)	44.05 (2.47)	44.15 (2.52)	44.23 (2.68)	40.51 (4.09)	40.81 (4.11)	40.82 (4.15)
Median (min, max)	44.00 (37.0, 52.0)	44.00 (34.0, 50.0)	45.00 (37.0, 51.0)	41.00 (25.0, 56.0)	41.00 (24.0, 53.0)	41.00 (25.0, 57.7)

Baseline Characteristics	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Baseline creatinine (µmol/L)						
n	353	354	354	3723	2828	5051
Mean (SD)	88.87 (17.61)	88.85 (17.61)	88.11 (18.30)	86.76 (24.88)	87.10 (22.75)	88.93 (31.84)
Median (min, max)	88.40 (52.0, 185.6)	88.00 (53.0, 185.6)	85.50 (53.0, 176.0)	82.00 (29.0, 771.0)	83.00 (35.0, 345.0)	83.00 (21.0, 771.0)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

ADT: androgen deprivation therapy; BMI: body mass index; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; max: maximum; min: minimum; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Table 40. Baseline disease characteristics and medical history (Safety Groups)

Baseline Characteristics	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Disease stage at study entry per investigator, n (%)						
Nonmetastatic (M0)	352 (99.7)	353 (99.7)	353 (99.7)	1267 (34.0)	807 (28.5)	1798 (35.2)
Metastatic (M1)	1 (0.3)	1 (0.3)	1 (0.3)	2461 (66.0)	2022 (71.5)	3312 (64.8)
Baseline ECOG performance status, n (%)						
0	326 (92.4)	334 (94.4)	321 (90.7)	2512 (67.4)	2023 (71.5)	3504 (68.6)
1	26 (7.4)	19 (5.4)	33 (9.3)	1143 (30.7)	773 (27.3)	1453 (28.4)
2	1 (0.3)	0	0	71 (1.9)	32 (1.1)	83 (1.6)
≥ 3	0	0	0	0	0	2 (0.0)
Missing	0	1 (0.3)	0	2 (0.1)	1 (0.0)	68 (1.3)
Category of baseline pain score as assessed by BPI-SF question 3, n (%)						
0 to 1	210 (59.5)	219 (61.9)	206 (58.2)	2183 (58.6)	1738 (61.4)	3032 (59.3)
2 to 3	65 (18.4)	71 (20.1)	67 (18.9)	800 (21.5)	622 (22.0)	1097 (21.5)
4 to 10	51 (14.4)	41 (11.6)	54 (15.3)	605 (16.2)	375 (13.3)	755 (14.8)
Missing	27 (7.6)	23 (6.5)	27 (7.6)	140 (3.8)	94 (3.3)	226 (4.4)
Time from initial diagnosis to randomization, months						
n	353	354	354	3721	2820	5096
Mean (SD)	67.31 (44.35)	70.40 (48.99)	72.70 (52.10)	72.86 (59.06)	65.42 (56.72)	71.49 (59.06)
Median (min, max)	56.87 (5.8, 222.4)	64.36 (5.7, 305.5)	61.51 (6.0, 297.4)	59.80 (0.2, 381.8)	52.47 (0.1, 305.5)	58.06 (0.2, 400.7)
Total Gleason score at initial diagnosis§, n (%)						
Low (2 to 4)	1 (0.3)	0	3 (0.8)	41 (1.1)	30 (1.1)	52 (1.0)
Medium (5 to 7)	232 (65.7)	242 (68.4)	235 (66.4)	1703 (45.7)	1260 (44.5)	2373 (46.4)
High (8 to 10)	119 (33.7)	111 (31.4)	111 (31.4)	1814 (48.7)	1425 (50.4)	2438 (47.7)
Missing/unknown	1 (0.3)	1 (0.3)	5 (1.4)	170 (4.6)	114 (4.0)	247 (4.8)
Medical history of hypertension, n (%)						
Yes	212 (60.1)	220 (62.1)	214 (60.5)	2175 (58.3)	1674 (59.2)	3050 (59.7)
No	141 (39.9)	134 (37.9)	140 (39.5)	1553 (41.7)	1155 (40.8)	2060 (40.3)
Medical history of cardiovascular disease, n (%)						
Yes	52 (14.7)	49 (13.8)	54 (15.3)	700 (18.8)	510 (18.0)	965 (18.9)
No	301 (85.3)	305 (86.2)	300 (84.7)	3028 (81.2)	2319 (82.0)	4145 (81.1)
Medical history of diabetes, n (%)						
Yes	60 (17.0)	76 (21.5)	73 (20.6)	701 (18.8)	537 (19.0)	1001 (19.6)
No	293 (83.0)	278 (78.5)	281 (79.4)	3027 (81.2)	2292 (81.0)	4109 (80.4)
Medical history of hypercholesterolemia and/or hyperlipidemia, n (%)						
Yes	128 (36.3)	123 (34.7)	144 (40.7)	1037 (27.8)	813 (28.7)	1559 (30.5)
No	225 (63.7)	231 (65.3)	210 (59.3)	2691 (72.2)	2016 (71.3)	3551 (69.5)
Prior prostatectomy, n (%)						
Yes	268 (75.9)	251 (70.9)	265 (74.9)	1097 (29.4)	852 (30.1)	1625 (31.8)
No	85 (24.1)	103 (29.1)	89 (25.1)	2631 (70.6)	1977 (69.9)	3485 (68.2)
Prior orchiectomy, n (%)						
Yes	0	0	0	286 (7.7)	202 (7.1)	355 (6.9)
No	353 (100)	354 (100)	354 (100)	3442 (92.3)	2627 (92.9)	4755 (93.1)
Prior radiotherapy, n (%)						
Yes	264 (74.8)	281 (79.4)	255 (72.0)	1787 (47.9)	1312 (46.4)	2462 (48.2)
No	89 (25.2)	73 (20.6)	99 (28.0)	1941 (52.1)	1517 (53.6)	2648 (51.8)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory – Short Form; DB: double-blind; ECOG: Eastern Clinical Oncology Group; ENZA: enzalutamide; ISS: Integrated Summary of Safety; max: maximum; min: minimum; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ The Gleason score at initial diagnosis was provided if the primary and secondary Gleason scores were unavailable; otherwise, the score was calculated as the sum of the primary and secondary scores for those with primary and secondary scores. The unknown category was for patients with unknown primary, secondary and total Gleason scores.

Adverse events

Treatment-Emergent Adverse Events (TEAEs)

Table 41. Overall summary of Treatment-Emergent Adverse Events (TEAEs) (Safety Groups)

Category, n (%)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Any TEAE	343 (97.2)	345 (97.5)	347 (98.0)	3536 (94.8)	2576 (91.1)	4848 (94.9)
TEAE within the first 30 days	199/353 (56.4)	180/354 (50.8)	181/354 (51.1)	2193/3728 (58.8)	1578/2829 (55.8)	2866/5110 (56.1)
TEAE between 31 to 180 days	273/353 (77.3)	257/353 (72.8)	282/354 (79.7)	2803/3720 (75.3)	2031/2816 (72.1)	3762/5098 (73.8)
TEAE between 181 to 365 days	196/336 (58.3)	201/344 (58.4)	192/345 (55.7)	2061/3200 (64.4)	1034/1796 (57.6)	2732/4389 (62.2)
TEAE between 366 to 540 days	150/285 (52.6)	158/306 (51.6)	159/313 (50.8)	1400/2554 (54.8)	573/1183 (48.4)	1894/3530 (53.7)
TEAE between 541 to 730 days	151/285 (53.0)	160/293 (54.6)	180/305 (59.0)	1066/2027 (52.6)	324/735 (44.1)	1597/2880 (55.5)
TEAE between 731 to 900 days (2.5 years)	154/280 (55.0)	136/272 (50.0)	152/293 (51.9)	678/1521 (44.6)	190/425 (44.7)	1204/2414 (49.9)
TEAE between 2.5 to 3 years	146/270 (54.1)	127/255 (49.8)	163/285 (57.2)	408/1116 (36.6)	159/333 (47.7)	1029/2081 (49.4)
TEAE between 3 to 4 years	168/260 (64.6)	148/238 (62.2)	176/268 (65.7)	305/785 (38.9)	159/265 (60.0)	997/1790 (55.7)
TEAE between 4 to 5 years	147/244 (60.2)	127/205 (62.0)	140/238 (58.8)	163/504 (32.3)	127/207 (61.4)	554/1247 (44.4)
TEAE between 5 to 6 years	99/185 (53.5)	71/145 (49.0)	90/179 (50.3)	99/272 (36.4)	71/145 (49.0)	276/737 (37.4)
TEAE > 6 years	40/84 (47.6)	31/63 (49.2)	42/81 (51.9)	40/99 (40.4)	31/63 (49.2)	116/328 (35.4)
TEAE leading to study drug discontinuation§	60 (17.0)	32 (9.0)	55 (15.5)	596 (16.0)	437 (15.4)	979 (19.2)
TEAE leading to dose interruption	56 (15.9)	43 (12.1)	66 (18.6)	541 (14.5)	290 (10.3)	829 (16.2)
TEAE leading to dose reduction	25 (7.1)	16 (4.5)	56 (15.8)	208 (5.6)	67 (2.4)	352 (6.9)
Grade ≥ 3 TEAE	164 (46.5)	151 (42.7)	177 (50.0)	1616 (43.3)	1034 (36.6)	2454 (48.0)
Grade ≥ 3 TEAE within the first 30 days	11/353 (3.1)	9/354 (2.5)	11/354 (3.1)	219/3728 (5.9)	183/2829 (6.5)	318/5110 (6.2)
Grade ≥ 3 TEAE between 31 to 180 days	41/353 (11.6)	35/353 (9.9)	26/354 (7.3)	638/3720 (17.2)	567/2816 (20.1)	866/5098 (17.0)
Grade ≥ 3 TEAE between 181 to 365 days	30/336 (8.9)	26/344 (7.6)	27/345 (7.8)	474/3200 (14.8)	228/1796 (12.7)	627/4389 (14.3)
Grade ≥ 3 TEAE between 366 to 540 days	17/285 (6.0)	22/306 (7.2)	25/313 (8.0)	304/2554 (11.9)	118/1183 (10.0)	411/3530 (11.6)
Grade ≥ 3 TEAE between 541 to 730 days	21/285 (7.4)	27/293 (9.2)	25/305 (8.2)	236/2027 (11.6)	61/735 (8.3)	357/2880 (12.4)
Grade ≥ 3 TEAE between 731 to 900 days (2.5 years)	25/280 (8.9)	18/272 (6.6)	26/293 (8.9)	155/1521 (10.2)	26/425 (6.1)	277/2414 (11.5)
Grade ≥ 3 TEAE between 2.5 to 3 years	26/270 (9.6)	22/255 (8.6)	26/285 (9.1)	86/1116 (7.7)	30/333 (9.0)	222/2081 (10.7)
Grade ≥ 3 TEAE between 3 to 4 years	37/260 (14.2)	31/238 (13.0)	44/268 (16.4)	77/785 (9.8)	33/265 (12.5)	256/1790 (14.3)
Grade ≥ 3 TEAE between 4 to 5 years	37/244 (15.2)	25/205 (12.2)	38/238 (16.0)	43/504 (8.5)	25/207 (12.1)	154/1247 (12.3)
Grade ≥ 3 TEAE between 5 to 6 years	24/185 (13.0)	14/145 (9.7)	21/179 (11.7)	24/272 (8.8)	14/145 (9.7)	66/737 (9.0)
Grade ≥ 3 TEAE > 6 years	14/84 (16.7)	7/63 (11.1)	10/81 (12.3)	14/99 (14.1)	7/63 (11.1)	39/328 (11.9)
Serious TEAE	123 (34.8)	112 (31.6)	131 (37.0)	1277 (34.3)	781 (27.6)	1971 (38.6)
Grade ≥ 3 serious TEAE	110 (31.2)	100 (28.2)	116 (32.8)	1113 (29.9)	676 (23.9)	1733 (33.9)
TEAE leading to death	6 (1.7)	3 (0.8)	8 (2.3)	158 (4.2)	72 (2.5)	288 (5.6)
Drug-related TEAE¶	307 (87.0)	286 (80.8)	314 (88.7)	2491 (66.8)	1526 (53.9)	3413 (66.8)
Drug-related grade ≥ 3 TEAE¶	62 (17.6)	31 (8.8)	57 (16.1)	462 (12.4)	209 (7.4)	680 (13.3)
Drug-related serious TEAE¶	26 (7.4)	8 (2.3)	17 (4.8)	172 (4.6)	87 (3.1)	279 (5.5)
Drug-related TEAEs leading to death¶	0	0	0	6 (0.2)	2 (0.1)	13 (0.3)
Grade 3 or 4 TEAE	164 (46.5)	149 (42.1)	175 (49.4)	1570 (42.1)	1015 (35.9)	2376 (46.5)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) reporting at least 1 event and percentage of patients (%) are shown. NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; CRF: case report form; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ TEAE leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

¶ Drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug.

In the EMBARK study, **ischemic heart disease** occurred in 5.4% of patients treated with enzalutamide plus leuprolide and 9% of patients treated with enzalutamide as monotherapy. **Gynaecomastia** (all grades) was observed in 29 of 353 patients (8.2%) who were treated with enzalutamide plus leuprolide and 159 of 354 patients (44.9%) who were treated with enzalutamide as monotherapy. **Nipple pain** (all grades) was observed in 11 of 353 patients (3.1%) who were treated with enzalutamide plus leuprolide and 54 of 354 patients (15.3%) who were treated with enzalutamide as monotherapy. **Breast tenderness** (all grades) was observed in 5 of 353 patients (1.4%) who were treated with enzalutamide plus leuprolide and 51 of 354 patients (14.4%) who were treated with enzalutamide as monotherapy.

Study treatment was suspended in the EMBARK study for patients who had undetectable PSA at week 36, a modified treatment-emergent period was defined for the generation of additional TEAE analyses.

- For patients in the EMBARK study whose treatment was suspended due to undetectable PSA at week 36, the modified treatment-emergent period was defined as the period of time of study drug exposure starting from the date of the first dose of study drug through 30 days after last dose prior to the treatment suspension plus the time period starting from the date of first dose at study drug reinitiation through a minimum of 30 days after the last dose of study treatment, or 1 day prior to the start day of new antineoplastic drug therapy. If the date of first dose at study drug reinitiation was earlier than 30 days after last dose prior to the treatment suspension, then the modified treatment-emergent period was the same as the treatment-emergent period.
- For patients whose treatment was suspended due to undetectable PSA at week 36, the modified treatment-emergent period was defined as the period of time of study drug exposure starting from the date of the first dose of study drug through 30 days after last dose prior to the treatment suspension plus the time period starting from date of first dose at study drug reinitiation through a minimum of 30 days after last dose of study treatment, or the start day of new antineoplastic drug therapy – 1 day. If the date of first dose at study drug reinitiation was earlier than 30 days after last dose prior to the treatment suspension, then the modified treatment-emergent period was the same as that on-treatment period.
- For all other patients (who never suspended their treatment due to having detectable PSA at week 36 in the EMBARK study or who were in other phase 2 or 3 studies), the modified treatment-emergent period was the same as the treatment-emergent period.

Table 42. Overall summary of Treatment-Emergent Adverse events using the modified treatment-emergent period for EMBARK (Safety Groups)

	EMBARK			Phase 3†		
Category, n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n =3728)	DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
Any TEAE	339 (96.0)	343 (96.9)	344 (97.2)	3532 (94.7)	2574 (91.0)	4841 (94.7)
TEAE leading to study drug discontinuation§	58 (16.4)	31 (8.8)	55 (15.5)	594 (15.9)	436 (15.4)	977 (19.1)
TEAE leading to dose interruption	56 (15.9)	43 (12.1)	66 (18.6)	541 (14.5)	290 (10.3)	829 (16.2)
TEAE leading to dose reduction	25 (7.1)	16 (4.5)	56 (15.8)	208 (5.6)	67 (2.4)	352 (6.9)
Grade ≥ 3 TEAE	135 (38.2)	132 (37.3)	155 (43.8)	1587 (42.6)	1015 (35.9)	2403 (47.0)
Serious TEAE	94 (26.6)	99 (28.0)	112 (31.6)	1248 (33.5)	768 (27.1)	1923 (37.6)
Grade ≥ 3 serious TEAE	85 (24.1)	87 (24.6)	100 (28.2)	1088 (29.2)	663 (23.4)	1692 (33.1)
TEAE leading to death	6 (1.7)	3 (0.8)	8 (2.3)	158 (4.2)	72 (2.5)	288 (5.6)
Drug-related TEAE¶	305 (86.4)	282 (79.7)	311 (87.9)	2489 (66.8)	1522 (53.8)	3408 (66.7)
Drug-related grade ≥ 3 TEAE¶	59 (16.7)	29 (8.2)	55 (15.5)	459 (12.3)	207 (7.3)	675 (13.2)
Drug-related serious TEAE¶	24 (6.8)	7 (2.0)	16 (4.5)	170 (4.6)	86 (3.0)	276 (5.4)
Drug-related TEAEs leading to death¶	0	0	0	6 (0.2)	2 (0.1)	13 (0.3)
Grade 3 or 4 TEAE	135 (38.2)	130 (36.7)	153 (43.2)	1541 (41.3)	996 (35.2)	2325 (45.5)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) reporting at least 1 event and percentage of patients (%) are shown. NCI-CTCAE v4.03.

The modified treatment-emergent period takes into account the protocol-defined treatment suspension due to undetectable PSA at week 36 in the EMBARK study. For studies other than EMBARK, the modified treatment-emergent period refers to the treatment-emergent period.

ADT: androgen deprivation therapy; AE: adverse event; CRF: case report form; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; PSA: prostate-specific antigen; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ TEAE leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

¶ Drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug.

Frequently reported TEAEs

Table 43. Treatment-Emergent Adverse Events experienced by ≥ 5% of patients in the EMBARK enzalutamide plus ADT or placebo plus ADT groups, by SOC and Preferred Term (Safety Groups)

SOC (MedDRA v25.1) Preferred Term, n (%)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Blood and Lymphatic System Disorders	25 (7.1)	12 (3.4)	17 (4.8)	333 (8.9)	227 (8.0)	502 (9.8)
Anaemia	**25 (7.1)**	**12 (3.4)**	17 (4.8)	333 (8.9)	227 (8.0)	502 (9.8)
Eye Disorders	17 (4.8)	20 (5.6)	22 (6.2)	82 (2.2)	39 (1.4)	146 (2.9)
Cataract	17 (4.8)	20 (5.6)	22 (6.2)	82 (2.2)	39 (1.4)	146 (2.9)
Gastrointestinal Disorders	110 (31.2)	70 (19.8)	108 (30.5)	1385 (37.2)	870 (30.8)	1849 (36.2)
Diarrhoea	**49 (13.9)**	**31 (8.8)**	46 (13.0)	534 (14.3)	306 (10.8)	705 (13.8)
Constipation	**46 (13.0)**	**31 (8.8)**	34 (9.6)	624 (16.7)	379 (13.4)	830 (16.2)
Nausea	**42 (11.9)**	**29 (8.2)**	54 (15.3)	704 (18.9)	475 (16.8)	931 (18.2)
General Disorders and Administration Site Conditions	191 (54.1)	159 (44.9)	202 (57.1)	1765 (47.3)	981 (34.7)	2417 (47.3)
Fatigue	**151 (42.8)**	**116 (32.8)**	165 (46.6)	1236 (33.2)	633 (22.4)	1733 (33.9)
Asthenia	**39 (11.0)**	**21 (5.9)**	39 (11.0)	445 (11.9)	228 (8.1)	579 (11.3)
Oedema peripheral	27 (7.6)	37 (10.5)	31 (8.8)	350 (9.4)	225 (8.0)	485 (9.5)
Infections and Infestations	98 (27.8)	99 (28.0)	112 (31.6)	677 (18.2)	435 (15.4)	1021 (20.0)
COVID-19	27 (7.6)	36 (10.2)	44 (12.4)	27 (0.7)	36 (1.3)	85 (1.7)
Urinary tract infection	27 (7.6)	26 (7.3)	37 (10.5)	231 (6.2)	165 (5.8)	364 (7.1)
Nasopharyngitis	25 (7.1)	22 (6.2)	31 (8.8)	231 (6.2)	128 (4.5)	338 (6.6)
Upper respiratory tract infection	21 (5.9)	25 (7.1)	22 (6.2)	145 (3.9)	97 (3.4)	211 (4.1)
Bronchitis	19 (5.4)	12 (3.4)	10 (2.8)	107 (2.9)	48 (1.7)	147 (2.9)
Injury, Poisoning and Procedural Complications	84 (23.8)	63 (17.8)	66 (18.6)	484 (13.0)	166 (5.9)	731 (14.3)
Fall	**74 (21.0)**	**51 (14.4)**	56 (15.8)	428 (11.5)	145 (5.1)	649 (12.7)
Rib fracture	29 (8.2)	23 (6.5)	20 (5.6)	140 (3.8)	43 (1.5)	200 (3.9)
Investigations	48 (13.6)	39 (11.0)	54 (15.3)	441 (11.8)	245 (8.7)	632 (12.4)
Weight increased	27 (7.6)	30 (8.5)	17 (4.8)	93 (2.5)	86 (3.0)	126 (2.5)
Weight decreased	**24 (6.8)**	**12 (3.4)**	39 (11.0)	352 (9.4)	164 (5.8)	512 (10.0)
Metabolism and Nutrition Disorders	44 (12.5)	32 (9.0)	40 (11.3)	630 (16.9)	361 (12.8)	827 (16.2)
Decreased appetite	**27 (7.6)**	**15 (4.2)**	32 (9.0)	604 (16.2)	335 (11.8)	791 (15.5)
Type 2 diabetes mellitus	17 (4.8)	18 (5.1)	10 (2.8)	28 (0.8)	27 (1.0)	42 (0.8)
Musculoskeletal and Connective Tissue Disorders	169 (47.9)	142 (40.1)	158 (44.6)	1539 (41.3)	975 (34.5)	2152 (42.1)
Arthralgia	**97 (27.5)**	**75 (21.2)**	81 (22.9)	843 (22.6)	464 (16.4)	1156 (22.6)
Back pain	60 (17.0)	54 (15.3)	62 (17.5)	706 (18.9)	454 (16.0)	1001 (19.6)
Pain in extremity	41 (11.6)	36 (10.2)	40 (11.3)	386 (10.4)	258 (9.1)	538 (10.5)
Osteoarthritis	21 (5.9)	15 (4.2)	19 (5.4)	77 (2.1)	34 (1.2)	134 (2.6)
Neck pain	16 (4.5)	18 (5.1)	14 (4.0)	94 (2.5)	77 (2.7)	152 (3.0)
Muscle spasms	14 (4.0)	19 (5.4)	9 (2.5)	104 (2.8)	79 (2.8)	138 (2.7)
Nervous System Disorders	84 (23.8)	69 (19.5)	86 (24.3)	709 (19.0)	331 (11.7)	997 (19.5)
Dizziness	39 (11.0)	37 (10.5)	41 (11.6)	337 (9.0)	171 (6.0)	490 (9.6)
Headache	**39 (11.0)**	**32 (9.0)**	41 (11.6)	373 (10.0)	161 (5.7)	506 (9.9)
Memory impairment	**26 (7.4)**	**12 (3.4)**	21 (5.9)	103 (2.8)	31 (1.1)	156 (3.1)
Psychiatric Disorders	73 (20.7)	63 (17.8)	56 (15.8)	491 (13.2)	252 (8.9)	700 (13.7)
Insomnia	42 (11.9)	37 (10.5)	25 (7.1)	269 (7.2)	150 (5.3)	369 (7.2)
Depression	21 (5.9)	20 (5.6)	21 (5.9)	139 (3.7)	63 (2.2)	213 (4.2)
Anxiety	**19 (5.4)**	**11 (3.1)**	18 (5.1)	150 (4.0)	61 (2.2)	216 (4.2)
Renal and Urinary Disorders	102 (28.9)	105 (29.7)	98 (27.7)	704 (18.9)	459 (16.2)	1000 (19.6)
Haematuria	42 (11.9)	44 (12.4)	45 (12.7)	299 (8.0)	180 (6.4)	449 (8.8)
Urinary incontinence	34 (9.6)	28 (7.9)	36 (10.2)	143 (3.8)	72 (2.5)	226 (4.4)
Pollakiuria	30 (8.5)	30 (8.5)	27 (7.6)	191 (5.1)	114 (4.0)	267 (5.2)

Nocturia	**26 (7.4)**	**16 (4.5)**	9 (2.5)	128 (3.4)	80 (2.8)	167 (3.3)
Dysuria	12 (3.4)	18 (5.1)	10 (2.8)	121 (3.2)	103 (3.6)	166 (3.2)
Reproductive System and Breast Disorders	29 (8.2)	32 (9.0)	159 (44.9)	136 (3.6)	66 (2.3)	329 (6.4)
Gynaecomastia	29 (8.2)	32 (9.0)	159 (44.9)	136 (3.6)	66 (2.3)	329 (6.4)
Respiratory, Thoracic and Mediastinal Disorders	59 (16.7)	49 (13.8)	52 (14.7)	513 (13.8)	307 (10.9)	701 (13.7)
Dyspnoea	30 (8.5)	25 (7.1)	19 (5.4)	259 (6.9)	161 (5.7)	357 (7.0)
Epistaxis	**19 (5.4)**	**2 (0.6)**	18 (5.1)	104 (2.8)	26 (0.9)	142 (2.8)
Cough	18 (5.1)	24 (6.8)	19 (5.4)	216 (5.8)	152 (5.4)	297 (5.8)
Skin and Subcutaneous Tissue Disorders	57 (16.1)	31 (8.8)	48 (13.6)	260 (7.0)	121 (4.3)	401 (7.8)
Dry skin	**22 (6.2)**	**10 (2.8)**	17 (4.8)	98 (2.6)	40 (1.4)	147 (2.9)
Rash	22 (6.2)	23 (6.5)	22 (6.2)	118 (3.2)	77 (2.7)	194 (3.8)
Alopecia	**19 (5.4)**	**4 (1.1)**	13 (3.7)	64 (1.7)	14 (0.5)	90 (1.8)
Vascular Disorders	265 (75.1)	232 (65.5)	126 (35.6)	1208 (32.4)	603 (21.3)	1574 (30.8)
Hot flush	**243 (68.8)**	**203 (57.3)**	77 (21.8)	863 (23.1)	481 (17.0)	1045 (20.5)
Hypertension	**82 (23.2)**	**69 (19.5)**	67 (18.9)	492 (13.2)	180 (6.4)	728 (14.2)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term or SOC were counted only once for each preferred term and SOC. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by SOC alphabetically and then by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

Preferred term frequencies highlighted in **bold** are TEAEs that occurred in ≥ 5% of patients in the EMBARK ENZA+ADT group and ≥ 2% higher incidence than the EMBARK PBO+ADT group.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

Grade ≥ 3 TEAEs

Table 44: Grade ≥ 3 Treatment-Emergent Adverse Events experienced by ≥ 1% of patients in the EMBARK enzalutamide plus ADT or placebo plus ADT groups, by Preferred Term (Safety Groups)

	EMBARK			Phase 3†		
Preferred Term (MedDRA v25.1), n (%)	**DB ENZA+ADT (n = 353)**	**DB PBO+ADT (n = 354)**	**ENZA Mono (n = 354)**	**DB ENZA+ADT (n = 3728)**	**DB PBO+ADT (n = 2829)**	**Total‡ ENZA±ADT (n = 5110)**
Patients with grade ≥ 3 TEAE§	164 (46.5)	151 (42.7)	177 (50.0)	1616 (43.3)	1034 (36.6)	2454 (48.0)
Hypertension	**24 (6.8)**	**18 (5.1)**	19 (5.4)	186 (5.0)	63 (2.2)	277 (5.4)
Syncope	**15 (4.2)**	**6 (1.7)**	7 (2.0)	60 (1.6)	21 (0.7)	86 (1.7)
Fatigue	**12 (3.4)**	**5 (1.4)**	14 (4.0)	126 (3.4)	59 (2.1)	180 (3.5)
Osteoarthritis	**10 (2.8)**	**2 (0.6)**	2 (0.6)	23 (0.6)	7 (0.2)	40 (0.8)
Haematuria	**8 (2.3)**	**4 (1.1)**	9 (2.5)	68 (1.8)	43 (1.5)	107 (2.1)
Pneumonia	**8 (2.3)**	**5 (1.4)**	5 (1.4)	71 (1.9)	30 (1.1)	117 (2.3)
Arthralgia	**7 (2.0)**	**1 (0.3)**	2 (0.6)	54 (1.4)	31 (1.1)	72 (1.4)
Anaemia	**5 (1.4)**	**3 (0.8)**	3 (0.8)	126 (3.4)	86 (3.0)	191 (3.7)
Atrial fibrillation	**5 (1.4)**	**3 (0.8)**	2 (0.6)	23 (0.6)	13 (0.5)	41 (0.8)
Sepsis	5 (1.4)	5 (1.4)	6 (1.7)	18 (0.5)	13 (0.5)	33 (0.6)
Angina pectoris	**4 (1.1)**	**1 (0.3)**	3 (0.8)	11 (0.3)	3 (0.1)	23 (0.5)
Arthritis	**4 (1.1)**	**1 (0.3)**	3 (0.8)	6 (0.2)	2 (0.1)	10 (0.2)
Coronary artery disease	**4 (1.1)**	**1 (0.3)**	5 (1.4)	16 (0.4)	4 (0.1)	27 (0.5)
Fall	4 (1.1)	4 (1.1)	7 (2.0)	43 (1.2)	17 (0.6)	80 (1.6)
Pulmonary embolism	**4 (1.1)**	**1 (0.3)**	2 (0.6)	26 (0.7)	22 (0.8)	36 (0.7)
Urinary incontinence	4 (1.1)	3 (0.8)	6 (1.7)	14 (0.4)	6 (0.2)	25 (0.5)
Cataract	3 (0.8)	5 (1.4)	8 (2.3)	31 (0.8)	12 (0.4)	51 (1.0)
Acute myocardial infarction	2 (0.6)	4 (1.1)	4 (1.1)	20 (0.5)	7 (0.2)	41 (0.8)
COVID-19	2 (0.6)	4 (1.1)	2 (0.6)	2 (0.1)	4 (0.1)	8 (0.2)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

Preferred term frequencies highlighted in **bold** are grade ≥ 3 TEAEs that occurred in ≥ 1% of patients in the EMBARK ENZA+ADT group and ≥ 0.5% higher incidence than the EMBARK PBO+ADT group.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Grade ≥ 3, based on National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.

In the EMBARK study, grade 3 or higher **gynaecomastia** was not observed in any patients who were treated with enzalutamide plus leuprolide, and was observed in 3 patients (0.8%) who were treated with enzalutamide as monotherapy. Grade 3 or higher **nipple pain** was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy. Grade 3 or higher **breast tenderness** was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Drug-related TEAEs

Table 45. Study Drug-related Treatment-Emergent Adverse Events experienced by ≥2% of patients in the EMBARK enzalutamide plus ADT or placebo plus ADT groups, by Preferred Term (Safety Groups)

	EMBARK			Phase 3†		
Preferred Term (MedDRA v25.1), n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
Patients with study drug-related TEAE§	307 (87.0)	286 (80.8)	314 (88.7)	2491 (66.8)	1526 (53.9)	3413 (66.8)
Hot flush	242 (68.6)	196 (55.4)	73 (20.6)	716 (19.2)	412 (14.6)	878 (17.2)
Fatigue	140 (39.7)	99 (28.0)	156 (44.1)	946 (25.4)	448 (15.8)	1363 (26.7)
Hypertension	46 (13.0)	29 (8.2)	38 (10.7)	230 (6.2)	79 (2.8)	343 (6.7)
Asthenia	33 (9.3)	14 (4.0)	33 (9.3)	280 (7.5)	122 (4.3)	365 (7.1)
Headache	25 (7.1)	15 (4.2)	27 (7.6)	164 (4.4)	62 (2.2)	223 (4.4)
Dizziness	24 (6.8)	16 (4.5)	25 (7.1)	166 (4.5)	67 (2.4)	239 (4.7)
Memory impairment	24 (6.8)	10 (2.8)	18 (5.1)	67 (1.8)	20 (0.7)	103 (2.0)
Gynaecomastia	23 (6.5)	28 (7.9)	152 (42.9)	96 (2.6)	49 (1.7)	274 (5.4)
Nausea	22 (6.2)	17 (4.8)	34 (9.6)	422 (11.3)	276 (9.8)	544 (10.6)
Decreased appetite	20 (5.7)	6 (1.7)	22 (6.2)	299 (8.0)	145 (5.1)	375 (7.3)
Diarrhoea	19 (5.4)	10 (2.8)	27 (7.6)	206 (5.5)	119 (4.2)	276 (5.4)
Insomnia	19 (5.4)	19 (5.4)	11 (3.1)	88 (2.4)	48 (1.7)	117 (2.3)
Weight increased	18 (5.1)	25 (7.1)	14 (4.0)	63 (1.7)	53 (1.9)	86 (1.7)
Alopecia	17 (4.8)	4 (1.1)	10 (2.8)	43 (1.2)	8 (0.3)	63 (1.2)
Fall	16 (4.5)	11 (3.1)	20 (5.6)	54 (1.4)	18 (0.6)	108 (2.1)
Dry skin	15 (4.2)	3 (0.8)	9 (2.5)	53 (1.4)	14 (0.5)	79 (1.5)
Libido decreased	15 (4.2)	11 (3.1)	14 (4.0)	17 (0.5)	12 (0.4)	32 (0.6)
Amnesia	14 (4.0)	2 (0.6)	13 (3.7)	31 (0.8)	5 (0.2)	60 (1.2)
Arthralgia	12 (3.4)	13 (3.7)	15 (4.2)	125 (3.4)	74 (2.6)	163 (3.2)
Constipation	12 (3.4)	5 (1.4)	6 (1.7)	158 (4.2)	83 (2.9)	192 (3.8)
Hyperhidrosis	12 (3.4)	4 (1.1)	5 (1.4)	55 (1.5)	31 (1.1)	72 (1.4)
Muscular weakness	11 (3.1)	11 (3.1)	5 (1.4)	57 (1.5)	36 (1.3)	84 (1.6)
Anaemia	10 (2.8)	4 (1.1)	2 (0.6)	71 (1.9)	47 (1.7)	87 (1.7)
Dyspnoea	10 (2.8)	7 (2.0)	3 (0.8)	53 (1.4)	31 (1.1)	70 (1.4)
Erectile dysfunction	10 (2.8)	11 (3.1)	12 (3.4)	15 (0.4)	15 (0.5)	30 (0.6)
Osteoporosis	10 (2.8)	1 (0.3)	0	23 (0.6)	6 (0.2)	36 (0.7)
Overdose	10 (2.8)	12 (3.4)	18 (5.1)	11 (0.3)	12 (0.4)	29 (0.6)
Anxiety	9 (2.5)	3 (0.8)	13 (3.7)	38 (1.0)	8 (0.3)	60 (1.2)
Pain in extremity	9 (2.5)	5 (1.4)	6 (1.7)	42 (1.1)	21 (0.7)	61 (1.2)
Rash	9 (2.5)	10 (2.8)	9 (2.5)	46 (1.2)	30 (1.1)	72 (1.4)
Back pain	8 (2.3)	1 (0.3)	8 (2.3)	45 (1.2)	27 (1.0)	67 (1.3)
Depression	8 (2.3)	9 (2.5)	9 (2.5)	41 (1.1)	15 (0.5)	63 (1.2)
Paraesthesia	8 (2.3)	1 (0.3)	6 (1.7)	42 (1.1)	8 (0.3)	56 (1.1)
Testicular atrophy	8 (2.3)	4 (1.1)	0	11 (0.3)	4 (0.1)	12 (0.2)
Lethargy	7 (2.0)	12 (3.4)	12 (3.4)	42 (1.1)	40 (1.4)	65 (1.3)
Oedema peripheral	6 (1.7)	16 (4.5)	11 (3.1)	109 (2.9)	62 (2.2)	144 (2.8)
Muscle spasms	5 (1.4)	8 (2.3)	2 (0.6)	33 (0.9)	35 (1.2)	42 (0.8)
Alanine aminotransferase increased	3 (0.8)	8 (2.3)	2 (0.6)	22 (0.6)	23 (0.8)	33 (0.6)
Aspartate aminotransferase increased	3 (0.8)	9 (2.5)	2 (0.6)	21 (0.6)	30 (1.1)	27 (0.5)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Study drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug. TEAEs could be related to any study drug (enzalutamide, placebo and/or leuprolide).

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Treatment-emergent SAEs

Table 46. Treatment-Emergent Serious Adverse Events experienced by ≥ 1% of patients in the EMBARK enzalutamide plus ADT or placebo plus ADT groups, by Preferred Term (Safety Groups)

Preferred Term (MedDRA v25.1), n (%) Event Rate†	EMBARK			Phase 3‡		Total§
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Overall	123 (34.8)	112 (31.6)	131 (37.0)	1277 (34.3)	781 (27.6)	1971 (38.6)
Syncope	9 (2.5)	4 (1.1)	2 (0.6)	31 (0.8)	9 (0.3)	44 (0.9)
Event rate per 100 patient-years (number of events)	0.7 (10)	0.3 (4)	0.2 (3)	0.4 (32)	0.3 (9)	0.4 (46)
Haematuria	8 (2.3)	4 (1.1)	8 (2.3)	68 (1.8)	44 (1.6)	108 (2.1)
Event rate per 100 patient-years (number of events)	0.9 (14)	0.4 (5)	0.6 (9)	1.2 (94)	1.4 (51)	1.2 (148)
Osteoarthritis	8 (2.3)	3 (0.8)	2 (0.6)	18 (0.5)	10 (0.4)	36 (0.7)
Event rate per 100 patient-years (number of events)	0.6 (9)	0.3 (4)	0.1 (2)	0.3 (19)	0.3 (11)	0.3 (37)
Pneumonia	8 (2.3)	4 (1.1)	5 (1.4)	67 (1.8)	24 (0.8)	110 (2.2)
Event rate per 100 patient-years (number of events)	0.5 (8)	0.5 (7)	0.3 (5)	1.0 (73)	0.8 (28)	1.0 (123)
Arthralgia	5 (1.4)	1 (0.3)	1 (0.3)	11 (0.3)	2 (0.1)	19 (0.4)
Event rate per 100 patient-years (number of events)	0.3 (5)	0.1 (1)	0.1 (1)	0.2 (12)	0.1 (2)	0.2 (20)
Atrial fibrillation	4 (1.1)	3 (0.8)	1 (0.3)	25 (0.7)	19 (0.7)	40 (0.8)
Event rate per 100 patient-years (number of events)	0.3 (4)	0.2 (3)	0.1 (2)	0.3 (26)	0.5 (19)	0.3 (43)
Sepsis	4 (1.1)	4 (1.1)	6 (1.7)	17 (0.5)	12 (0.4)	33 (0.6)
Event rate per 100 patient-years (number of events)	0.3 (4)	0.3 (4)	0.4 (7)	0.2 (18)	0.3 (12)	0.3 (36)
Transient ischaemic attack	4 (1.1)	2 (0.6)	2 (0.6)	19 (0.5)	9 (0.3)	32 (0.6)
Event rate per 100 patient-years (number of events)	0.3 (4)	0.1 (2)	0.1 (2)	0.3 (20)	0.3 (9)	0.3 (34)
Acute myocardial infarction	2 (0.6)	4 (1.1)	3 (0.8)	22 (0.6)	8 (0.3)	41 (0.8)
Event rate per 100 patient-years (number of events)	0.2 (3)	0.3 (4)	0.2 (3)	0.3 (25)	0.2 (8)	0.4 (46)
COVID-19	2 (0.6)	4 (1.1)	2 (0.6)	2 (0.1)	4 (0.1)	8 (0.2)
Event rate per 100 patient-years (number of events)	0.1 (2)	0.3 (4)	0.1 (2)	0.0 (2)	0.1 (4)	0.1 (8)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† Time-adjusted rate per 100 patient-years and number of events are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100.

‡ The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

§ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Deaths

Deaths include deaths occurring during and after the treatment-emergent safety reporting period. Death causes were classified as due to disease progression, due to other causes (than prostate cancer), or due to unknown (or unspecified) causes.

In the EMBARK study, disease progression and other causes were reported as the primary cause of death in a similar percentage of patients. No patients in the EMBARK study had a TEAE leading to death that was considered to be study drug-related.

Table 47. Summary of all deaths (Safety Groups)

Deaths, n (%)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Total number of deaths	33 (9.3)	55 (15.5)	42 (11.9)	1833 (49.2)	1549 (54.8)	2124 (41.6)
Cause of death						
Disease progression	12 (3.4)	22 (6.2)	19 (5.4)	1424 (38.2)	1248 (44.1)	1629 (31.9)
Other§	16 (4.5)	21 (5.9)	18 (5.1)	305 (8.2)	228 (8.1)	374 (7.3)
Unknown	5 (1.4)	12 (3.4)	5 (1.4)	104 (2.8)	70 (2.5)	121 (2.4)
Missing	0	0	0	0	3 (0.1)	0
Deaths within 30 days after the first dose date of study drug	0	0	0	4 (0.1)	4 (0.1)	10 (0.2)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

All deaths up to and including the analysis data cutoff date are included. Number of patients (n) and percentage of patients (%) are shown.

Table is based on data from the end-of-study case report form.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ All known primary causes of death other than disease progression.

Table 48. Treatment-Emergent Adverse Events resulting in death by Preferred Term in ≥ 2 patients in the total enzalutamide group, by Preferred Term and adjusted event rate (Safety Groups)

Preferred Term (MedDRA v25.1), n (%) Event Rate†	EMBARK			Phase 3‡		Total§
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Patients with ≥ 1 TEAE resulting in death	6 (1.7)	3 (0.8)	8 (2.3)	158 (4.2)	72 (2.5)	288 (5.6)
Total treatment-emergent period (patient-years)¶	1535.48	1423.11	1571.94	7571.16	3572.94	12585.63
Overall TEAE leading to death rate per 100 patient-years (number of events)	0.4 (6)	0.2 (3)	0.5 (8)	2.3 (171)	2.1 (76)	2.5 (314)
Disease progression	2 (0.6)	0	1 (0.3)	12 (0.3)	6 (0.2)	33 (0.6)
Event rate per 100 patient-years (number of events)	0.1 (2)	0	0.1 (1)	0.2 (12)	0.2 (6)	0.3 (33)
Aspiration	1 (0.3)	0	0	2 (0.1)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0.1 (1)	0	0	0.0 (2)	0	0.0 (2)
Death	1 (0.3)	0	3 (0.8)	12 (0.3)	4 (0.1)	16 (0.3)
Event rate per 100 patient-years (number of events)	0.1 (1)	0	0.2 (3)	0.2 (12)	0.1 (4)	0.1 (16)
Pneumonia	1 (0.3)	0	0	11 (0.3)	1 (0.0)	22 (0.4)
Event rate per 100 patient-years (number of events)	0.1 (1)	0	0	0.1 (11)	0.0 (1)	0.2 (22)
Sepsis	1 (0.3)	1 (0.3)	0	4 (0.1)	2 (0.1)	6 (0.1)
Event rate per 100 patient-years (number of events)	0.1 (1)	0.1 (1)	0	0.1 (4)	0.1 (2)	0.0 (6)
Acute kidney injury	0	0	0	0	2 (0.1)	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0	0.1 (2)	0.0 (3)
Acute myocardial infarction	0	0	0	5 (0.1)	0	9 (0.2)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (5)	0	0.1 (9)
Acute respiratory failure	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Anaemia	0	0	0	0	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0	0	0.0 (2)

Arteriosclerosis coronary artery	0	0	0	1 (0.0)	1 (0.0)	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0.0 (1)	0.0 (2)
Cachexia	0	0	0	2 (0.1)	1 (0.0)	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (2)	0.0 (1)	0.0 (2)
Cardiac arrest	0	0	1 (0.3)	3 (0.1)	2 (0.1)	5 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0.1 (1)	0.0 (3)	0.1 (2)	0.0 (5)
Cardiac failure	0	0	0	7 (0.2)	0	12 (0.2)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (7)	0	0.1 (12)
Cardiac failure congestive	0	0	0	0	1 (0.0)	4 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0	0.0 (1)	0.0 (4)
Cardio-respiratory arrest	0	0	0	2 (0.1)	1 (0.0)	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (2)	0.0 (1)	0.0 (3)
Cardiogenic shock	0	0	0	0	1 (0.0)	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0	0.0 (1)	0.0 (2)
Cardiopulmonary failure	0	0	0	4 (0.1)	0	5 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (4)	0	0.0 (5)
Cardiovascular insufficiency	0	0	0	0	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0	0	0.0 (2)
Cerebral infarction	0	0	1 (0.3)	1 (0.0)	0	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0.1 (1)	0.0 (1)	0	0.0 (3)
Cerebrovascular accident	0	0	0	5 (0.1)	1 (0.0)	5 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (5)	0.0 (1)	0.0 (5)
Circulatory collapse	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Coronary artery disease	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
COVID-19	0	0	1 (0.3)	0	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0.1 (1)	0	0	0.0 (2)
Disseminated intravascular coagulation	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Drowning	0	0	0	2 (0.1)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (2)	0	0.0 (2)
Gastric cancer	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
General physical health deterioration	0	0	0	19 (0.5)	10 (0.4)	25 (0.5)
Event rate per 100 patient-years (number of events)	0	0	0	0.3 (19)	0.3 (10)	0.2 (25)
Haemorrhage intracranial	0	0	0	0	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0	0	0.0 (2)
Hepatic failure	0	0	0	2 (0.1)	0	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (2)	0	0.0 (3)
Infection	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Malignant neoplasm progression	0	0	0	4 (0.1)	2 (0.1)	10 (0.2)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (4)	0.1 (2)	0.1 (10)
Metastases to liver	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Multiple organ dysfunction syndrome	0	0	0	1 (0.0)	1 (0.0)	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0.0 (1)	0.0 (3)

Myocardial infarction	0	0	1 (0.3)	7 (0.2)	1 (0.0)	10 (0.2)
Event rate per 100 patient-years (number of events)	0	0	0.1 (1)	0.1 (7)	0.0 (1)	0.1 (10)
Pneumonia aspiration	0	0	0	1 (0.0)	0	3 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (3)
Prostate cancer	0	0	0	1 (0.0)	0	5 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (5)
Prostate cancer metastatic	0	0	0	0	2 (0.1)	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0	0.1 (2)	0.0 (2)
Pulmonary embolism	0	0	0	5 (0.1)	1 (0.0)	7 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (5)	0.0 (1)	0.1 (7)
Septic shock	0	0	0	5 (0.1)	2 (0.1)	6 (0.1)
Event rate per 100 patient-years (number of events)	0	0	0	0.1 (5)	0.1 (2)	0.0 (6)
Subdural haematoma	0	0	0	1 (0.0)	1 (0.0)	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0.0 (1)	0.0 (2)
Urosepsis	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)
Ventricular fibrillation	0	0	0	1 (0.0)	0	2 (0.0)
Event rate per 100 patient-years (number of events)	0	0	0	0.0 (1)	0	0.0 (2)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† Time-adjusted rate per 100 patient-years and number of events are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100.

‡ The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

§ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

¶ Total treatment-emergent period in 100 patient-years for each treatment group is calculated as the sum of each patient's length of treatment-emergent period in days for each treatment group divided by 365.25.

No patients treated with enzalutamide plus leuprolide and one (0.3%) patient treated with enzalutamide as monotherapy had an **ischemic heart disease** event that led to death.

Other significant events: AEs of special interest (AESI)

TEAEs of special interest were selected based on previously recognized risks and/or feedback from regulatory authorities recommending surveillance for specific events. The prespecified TEAEs of special interest are convulsions (seizure), hypertension, neutrophil count decreased, cognitive and memory impairment, ischemic heart disease, other selected cardiovascular events, posterior reversible encephalopathy syndrome (PRES), fatigue, renal disorder, second primary malignancies, fall, fracture, loss of consciousness, thrombocytopenia, musculoskeletal events, severe cutaneous adverse reactions, angioedema, rash and hepatic disorder.

Table 49. Overall summary of prespecified treatment-emergent AESIs (Safety Groups)

	EMBARK			Phase 3‡		
Category†, n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total§ ENZA±ADT (n = 5110)
Convulsions (seizure)	4 (1.1)	0	3 (0.8)	16 (0.4)	4 (0.1)	31 (0.6)
Hypertension	89 (25.2)	74 (20.9)	77 (21.8)	522 (14.0)	199 (7.0)	788 (15.4)
Neutrophil count decreased	4 (1.1)	8 (2.3)	3 (0.8)	52 (1.4)	20 (0.7)	70 (1.4)
Cognitive and memory impairment	53 (15.0)	23 (6.5)	50 (14.1)	238 (6.4)	68 (2.4)	381 (7.5)
Ischemic heart disease	19 (5.4)	20 (5.6)	32 (9.0)	129 (3.5)	57 (2.0)	233 (4.6)
Other selected cardiovascular events	18 (5.1)	17 (4.8)	13 (3.7)	155 (4.2)	70 (2.5)	277 (5.4)
Posterior reversible encephalopathy syndrome	0	0	0	0	0	0
Fatigue	178 (50.4)	134 (37.9)	191 (54.0)	1608 (43.1)	837 (29.6)	2203 (43.1)
Renal disorder	21 (5.9)	10 (2.8)	14 (4.0)	132 (3.5)	105 (3.7)	213 (4.2)
Second primary malignancies	23 (6.5)	18 (5.1)	19 (5.4)	115 (3.1)	49 (1.7)	200 (3.9)
Fall	74 (21.0)	51 (14.4)	56 (15.8)	428 (11.5)	145 (5.1)	649 (12.7)
Fracture	65 (18.4)	48 (13.6)	39 (11.0)	457 (12.3)	163 (5.8)	640 (12.5)
Loss of consciousness	20 (5.7)	12 (3.4)	12 (3.4)	111 (3.0)	37 (1.3)	167 (3.3)
Thrombocytopenia	4 (1.1)	7 (2.0)	4 (1.1)	54 (1.4)	39 (1.4)	83 (1.6)
Musculoskeletal events	163 (46.2)	148 (41.8)	158 (44.6)	1630 (43.7)	1069 (37.8)	2249 (44.0)
Severe cutaneous adverse reactions	1 (0.3)	0	0	6 (0.2)	3 (0.1)	8 (0.2)
Angioedema	9 (2.5)	5 (1.4)	7 (2.0)	58 (1.6)	23 (0.8)	80 (1.6)
Rash	29 (8.2)	27 (7.6)	30 (8.5)	170 (4.6)	92 (3.3)	264 (5.2)
Hepatic disorder	17 (4.8)	32 (9.0)	13 (3.7)	103 (2.8)	118 (4.2)	165 (3.2)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) reporting at least 1 event and percentage of patients (%) are shown.

ADT: androgen deprivation therapy; AESI: adverse event of special interest; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† Definitions for all prespecified treatment-emergent AESIs are presented in [Table 3].

‡ The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

§ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Modified treatment-emergent Period

Table 50. Overall summary of prespecified treatment-emergent adverse events of special interest using the modified treatment-emergent period (EMBARK study, Safety Population)

	EMBARK			Phase 3‡		
Category†, n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total§ ENZA±ADT (n = 5110)
Convulsions (seizure)	4 (1.1)	0	3 (0.8)	16 (0.4)	4 (0.1)	31 (0.6)
Hypertension	77 (21.8)	61 (17.2)	61 (17.2)	510 (13.7)	186 (6.6)	760 (14.9)
Neutrophil count decreased	4 (1.1)	7 (2.0)	2 (0.6)	52 (1.4)	19 (0.7)	69 (1.4)
Cognitive and memory impairment	51 (14.4)	22 (6.2)	47 (13.3)	236 (6.3)	67 (2.4)	376 (7.4)
Ischemic heart disease	14 (4.0)	18 (5.1)	28 (7.9)	124 (3.3)	55 (1.9)	224 (4.4)
Other selected cardiovascular events	17 (4.8)	11 (3.1)	12 (3.4)	154 (4.1)	64 (2.3)	275 (5.4)
Posterior reversible encephalopathy syndrome	0	0	0	0	0	0
Fatigue	176 (49.9)	131 (37.0)	187 (52.8)	1606 (43.1)	834 (29.5)	2197 (43.0)
Renal disorder	13 (3.7)	9 (2.5)	9 (2.5)	124 (3.3)	104 (3.7)	200 (3.9)
Second primary malignancies	18 (5.1)	16 (4.5)	19 (5.4)	110 (3.0)	47 (1.7)	195 (3.8)
Fall	58 (16.4)	46 (13.0)	49 (13.8)	412 (11.1)	140 (4.9)	626 (12.3)
Fracture	49 (13.9)	35 (9.9)	33 (9.3)	441 (11.8)	150 (5.3)	618 (12.1)
Loss of consciousness	14 (4.0)	11 (3.1)	11 (3.1)	105 (2.8)	36 (1.3)	160 (3.1)
Thrombocytopenia	3 (0.8)	7 (2.0)	3 (0.8)	53 (1.4)	39 (1.4)	81 (1.6)
Musculoskeletal events	126 (35.7)	131 (37.0)	137 (38.7)	1593 (42.7)	1052 (37.2)	2191 (42.9)
Severe cutaneous adverse reactions	1 (0.3)	0	0	6 (0.2)	3 (0.1)	8 (0.2)
Angioedema	7 (2.0)	5 (1.4)	5 (1.4)	56 (1.5)	23 (0.8)	76 (1.5)
Rash	22 (6.2)	22 (6.2)	27 (7.6)	163 (4.4)	87 (3.1)	254 (5.0)
Hepatic disorder	11 (3.1)	23 (6.5)	7 (2.0)	97 (2.6)	109 (3.9)	153 (3.0)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) reporting at least 1 event and percentage of patients (%) are shown.

The modified treatment-emergent period takes into account the protocol-defined treatment suspension due to undetectable PSA at week 36 in the EMBARK study. For studies other than EMBARK, the modified treatment-emergent period refers to the treatment-emergent period.

ADT: androgen deprivation therapy; AESI: adverse event of special interest; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; PSA: prostate-specific antigen; SCS: Summary of Clinical Safety.

† Definitions for all prespecified treatment-emergent AESIs are presented in [Table 3].

‡ The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

§ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

- *Ischemic heart disease*

Table 51. Treatment-Emergent Adverse Events of Ischemic Heart Disease for ≥ 1 patient in the EMBARK enzalutamide plus ADT group by Preferred Term (Safety Groups)

Preferred Term (MedDRA v25.1) Category, n (%) Event Rate (events)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Any event of ischemic heart disease Event rate (e)	19 (5.4) 2.1 (33)	20 (5.6) 1.7 (24)	32 (9.0) 2.5 (39)	129 (3.5) 2.2 (163)	57 (2.0) 1.9 (68)	233 (4.6) 2.4 (296)
Angina pectoris Event rate (e)	9 (2.5) 0.7 (11)	9 (2.5) 0.8 (11)	9 (2.5) 0.6 (10)	37 (1.0) 0.5 (40)	18 (0.6) 0.6 (22)	64 (1.3) 0.6 (74)
Coronary artery disease Event rate (e)	6 (1.7) 0.4 (6)	1 (0.3) 0.1 (1)	11 (3.1) 0.7 (11)	32 (0.9) 0.4 (33)	5 (0.2) 0.1 (5)	51 (1.0) 0.4 (52)
Acute coronary syndrome Event rate (e)	3 (0.8) 0.2 (3)	1 (0.3) 0.1 (1)	2 (0.6) 0.1 (2)	14 (0.4) 0.2 (14)	7 (0.2) 0.2 (7)	23 (0.5) 0.2 (23)
Coronary artery occlusion Event rate (e)	3 (0.8) 0.2 (3)	1 (0.3) 0.1 (1)	1 (0.3) 0.1 (1)	3 (0.1) 0.0 (3)	1 (0.0) 0.0 (1)	4 (0.1) 0.0 (4)
Myocardial infarction Event rate (e)	3 (0.8) 0.2 (3)	2 (0.6) 0.1 (2)	5 (1.4) 0.3 (5)	19 (0.5) 0.3 (19)	8 (0.3) 0.2 (8)	37 (0.7) 0.3 (37)
Acute myocardial infarction Event rate (e)	2 (0.6) 0.2 (3)	4 (1.1) 0.3 (4)	4 (1.1) 0.3 (4)	22 (0.6) 0.3 (25)	8 (0.3) 0.2 (8)	43 (0.8) 0.4 (48)
Angina unstable Event rate (e)	1 (0.3) 0.1 (2)	0	0	5 (0.1) 0.1 (7)	3 (0.1) 0.1 (3)	7 (0.1) 0.1 (9)
Coronary artery stenosis Event rate (e)	1 (0.3) 0.1 (1)	0	3 (0.8) 0.2 (3)	3 (0.1) 0.0 (3)	0	9 (0.2) 0.1 (9)
Myocardial ischaemia Event rate (e)	1 (0.3) 0.1 (1)	3 (0.8) 0.2 (3)	1 (0.3) 0.1 (1)	9 (0.2) 0.1 (9)	8 (0.3) 0.2 (8)	17 (0.3) 0.1 (17)
Any event of ischemic heart disease leading to death	0	1 (0.3)	1 (0.3)	14 (0.4)	3 (0.1)	23 (0.5)
Any serious event of ischemic heart disease	13 (3.7)	11 (3.1)	23 (6.5)	81 (2.2)	32 (1.1)	158 (3.1)
Any drug-related event of ischemic heart disease§	5 (1.4)	6 (1.7)	8 (2.3)	18 (0.5)	14 (0.5)	40 (0.8)
Any grade ≥ 3 event of ischemic heart disease	14 (4.0)	11 (3.1)	21 (5.9)	75 (2.0)	33 (1.2)	149 (2.9)
Any event of ischemic heart disease leading to study drug discontinuation¶	2 (0.6)	4 (1.1)	4 (1.1)	10 (0.3)	7 (0.2)	23 (0.5)
Any event of ischemic heart disease leading to dose interruption	2 (0.6)	4 (1.1)	5 (1.4)	22 (0.6)	12 (0.4)	40 (0.8)
Any event of ischemic heart disease leading to dose reduction	1 (0.3)	0	1 (0.3)	1 (0.0)	1 (0.0)	3 (0.1)
Any event of ischemic heart disease						
Within the first 30 days	0/353	0/354	1/354 (0.3)	2/3728 (0.1)	6/2829 (0.2)	4/5110 (0.1)
Between 31 to 180 days	1/353 (0.3)	3/353 (0.8)	0/354	33/3720 (0.9)	17/2816 (0.6)	40/5098 (0.8)
Between 181 to 365 days	2/336 (0.6)	4/344 (1.2)	6/345 (1.7)	29/3200 (0.9)	10/1796 (0.6)	45/4389 (1.0)
Between 366 to 540 days	1/285 (0.4)	3/306 (1.0)	2/313 (0.6)	16/2554 (0.6)	12/1183 (1.0)	28/3530 (0.8)
Between 541 to 730 days	2/285 (0.7)	1/293 (0.3)	3/305 (1.0)	20/2027 (1.0)	3/735 (0.4)	34/2880 (1.2)
Between 731 to 900 days (2.5 years)	2/280 (0.7)	2/272 (0.7)	6/293 (2.0)	14/1521 (0.9)	2/425 (0.5)	30/2414 (1.2)
Between 2.5 years to 3 years	2/270 (0.7)	4/255 (1.6)	4/285 (1.4)	11/1116 (1.0)	5/333 (1.5)	23/2081 (1.1)
Between 3 years to 4 years	4/260 (1.5)	2/238 (0.8)	9/268 (3.4)	7/785 (0.9)	2/265 (0.8)	33/1790 (1.8)
Between 4 years to 5 years	4/244 (1.6)	2/205 (1.0)	2/238 (0.8)	6/504 (1.2)	2/207 (1.0)	12/1247 (1.0)
Between 5 years to 6 years	1/185 (0.5)	2/145 (1.4)	2/179 (1.1)	1/272 (0.4)	2/145 (1.4)	8/737 (1.1)
> 6 years	3/84 (3.6)	0/63	1/81 (1.2)	3/99 (3.0)	0/63	7/328 (2.1)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

"Any event of ischemic heart disease" refers to AEs in the narrow SMQs of 'myocardial infarction' and 'other ischemic heart disease.'

Time-adjusted rate per 100 patient-years and number of events (e) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

Number of patients (n) reporting at least 1 event of ischemic heart disease and percentage of patients (%) are shown. NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; CRF: case report form; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug.

¶ Ischemic heart disease leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

- *Cognitive and memory impairment*

Table 52. Treatment-Emergent Adverse Events of Cognitive and Memory Impairment (Safety Groups)

Preferred Term (MedDRA v25.1) Category, n (%) Event Rate (events)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Any event of cognitive and memory impairment Event rate (e)	53 (15.0) 4.1 (63)	23 (6.5) 1.9 (27)	50 (14.1) 4.1 (64)	238 (6.4) 3.6 (271)	68 (2.4) 2.1 (74)	381 (7.5) 3.5 (444)
Memory impairment Event rate (e)	26 (7.4) 1.9 (29)	12 (3.4) 0.9 (13)	21 (5.9) 1.4 (22)	103 (2.8) 1.4 (108)	31 (1.1) 0.9 (32)	156 (3.1) 1.3 (163)
Amnesia Event rate (e)	17 (4.8) 1.2 (18)	8 (2.3) 0.6 (8)	16 (4.5) 1.1 (18)	61 (1.6) 0.8 (62)	15 (0.5) 0.4 (15)	109 (2.1) 0.9 (114)
Disturbance in attention Event rate (e)	8 (2.3) 0.5 (8)	2 (0.6) 0.2 (3)	11 (3.1) 0.7 (11)	44 (1.2) 0.6 (46)	10 (0.4) 0.3 (11)	71 (1.4) 0.6 (73)
Cognitive disorder Event rate (e)	2 (0.6) 0.3 (4)	1 (0.3) 0.1 (1)	8 (2.3) 0.5 (8)	33 (0.9) 0.5 (35)	8 (0.3) 0.2 (8)	56 (1.1) 0.5 (59)
Mental impairment Event rate (e)	2 (0.6) 0.1 (2)	0	2 (0.6) 0.1 (2)	3 (0.1) 0.0 (3)	1 (0.0) 0.0 (1)	6 (0.1) 0.0 (6)
Dementia Alzheimer's type Event rate (e)	1 (0.3) 0.1 (1)	0	3 (0.8) 0.2 (3)	7 (0.2) 0.1 (7)	1 (0.0) 0.0 (1)	12 (0.2) 0.1 (12)
Vascular dementia Event rate (e)	1 (0.3) 0.1 (1)	0	0	2 (0.1) 0.0 (2)	0	2 (0.0) 0.0 (2)
Dementia Event rate (e)	0	2 (0.6) 0.1 (2)	0	5 (0.1) 0.1 (5)	6 (0.2) 0.2 (6)	11 (0.2) 0.1 (11)
Senile dementia Event rate (e)	0	0	0	2 (0.1) 0.0 (2)	0	3 (0.1) 0.0 (3)
Transient global amnesia Event rate (e)	0	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Any event of cognitive and memory impairment leading to death	0	0	0	0	1 (0.0)	1 (0.0)
Any serious event of cognitive and memory impairment	1 (0.3)	1 (0.3)	0	4 (0.1)	6 (0.2)	9 (0.2)
Any drug-related event of cognitive and memory impairment§	44 (12.5)	15 (4.2)	42 (11.9)	142 (3.8)	36 (1.3)	237 (4.6)
Any grade ≥ 3 event of cognitive and memory impairment	2 (0.6)	2 (0.6)	0	9 (0.2)	6 (0.2)	17 (0.3)
Any event of cognitive and memory impairment leading to study drug discontinuation¶	7 (2.0)	3 (0.8)	3 (0.8)	22 (0.6)	6 (0.2)	30 (0.6)
Any event of cognitive and memory impairment leading to dose interruption	3 (0.8)	3 (0.8)	1 (0.3)	12 (0.3)	5 (0.2)	17 (0.3)
Any event of cognitive and memory impairment leading to dose reduction	4 (1.1)	3 (0.8)	2 (0.6)	8 (0.2)	4 (0.1)	13 (0.3)
Any event of cognitive and memory impairment						
Within the first 30 days	13/353 (3.7)	7/354 (2.0)	5/354 (1.4)	55/3728 (1.5)	17/2829 (0.6)	70/5110 (1.4)
Between 31 to 180 days	23/353 (6.5)	5/353 (1.4)	15/354 (4.2)	85/3720 (2.3)	24/2816 (0.9)	119/5098 (2.3)
Between 181 to 365 days	4/336 (1.2)	5/344 (1.5)	8/345 (2.3)	49/3200 (1.5)	17/1796 (0.9)	72/4389 (1.6)
Between 366 to 540 days	0/285	2/306 (0.7)	5/313 (1.6)	19/2554 (0.7)	5/1183 (0.4)	32/3530 (0.9)
Between 541 to 730 days	2/285 (0.7)	3/293 (1.0)	8/305 (2.6)	24/2027 (1.2)	5/735 (0.7)	40/2880 (1.4)
Between 731 to 900 days (2.5 years)	5/280 (1.8)	2/272 (0.7)	2/293 (0.7)	10/1521 (0.7)	2/425 (0.5)	23/2414 (1.0)
Between 2.5 years to 3 years	2/270 (0.7)	1/255 (0.4)	3/285 (1.1)	10/1116 (0.9)	1/333 (0.3)	25/2081 (1.2)
Between 3 years to 4 years	7/260 (2.7)	2/238 (0.8)	10/268 (3.7)	12/785 (1.5)	2/265 (0.8)	39/1790 (2.2)
Between 4 years to 5 years	3/244 (1.2)	1/205 (0.5)	2/238 (0.8)	4/504 (0.8)	1/207 (0.5)	9/1247 (0.7)
Between 5 years to 6 years	3/185 (1.6)	0/145	2/179 (1.1)	3/272 (1.1)	0/145	7/737 (0.9)
> 6 years	1/84 (1.2)	0/63	0/81	1/99 (1.0)	0/63	2/328 (0.6)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

"Any event of cognitive and memory impairment" refers to all preferred terms in the MedDRA High Level Group Term of 'mental impairment disorders.'

Time-adjusted rate per 100 patient-years and number of events (e) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

Number of patients (n) reporting at least 1 event of cognitive and memory impairment and percentage of patients (%) are shown. NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; CRF: case report form; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug.

¶ Cognitive and memory impairment leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

- *Secondary Primary Malignancies*

Table 53.Treatment-emergent Adverse Events of Second Primary Malignancy, Excluding Nonmelanoma Skin Cancer for ≥ 1 Patient (Safety Groups)

Preferred Term (MedDRA v25.1) Category, n (%) Event Rate (events)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Any second primary malignancy, excluding nonmelanoma skin cancer	23 (6.5)	18 (5.1)	19 (5.4)	115 (3.1)	49 (1.7)	200 (3.9)
Event rate (e)	1.6 (25)	1.8 (25)	1.5 (24)	1.7 (127)	1.8 (63)	1.8 (225)
Malignant melanoma in situ Event rate (e)	3 (0.8) 0.2 (3)	0	1 (0.3) 0.1 (2)	4 (0.1) 0.1 (4)	1 (0.0) 0.0 (1)	5 (0.1) 0.0 (6)
Colon cancer Event rate (e)	2 (0.6) 0.1 (2)	0	0	6 (0.2) 0.1 (6)	3 (0.1) 0.1 (3)	11 (0.2) 0.1 (11)
Rectal cancer Event rate (e)	2 (0.6) 0.1 (2)	0	0	4 (0.1) 0.1 (4)	0	4 (0.1) 0.0 (4)
Adenocarcinoma gastric Event rate (e)	1 (0.3) 0.1 (1)	0	0	3 (0.1) 0.0 (3)	0	3 (0.1) 0.0 (3)
Adenocarcinoma of colon Event rate (e)	1 (0.3) 0.1 (1)	0	0	9 (0.2) 0.1 (9)	3 (0.1) 0.1 (3)	10 (0.2) 0.1 (10)
Bladder cancer Event rate (e)	1 (0.3) 0.1 (1)	0	0	10 (0.3) 0.1 (10)	0	13 (0.3) 0.1 (13)
Colon cancer metastatic Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	2 (0.0) 0.0 (2)
Diffuse large B-cell lymphoma Event rate (e)	1 (0.3) 0.1 (1)	0	0	2 (0.1) 0.0 (2)	1 (0.0) 0.0 (1)	2 (0.0) 0.0 (2)
Hepatocellular carcinoma Event rate (e)	1 (0.3) 0.1 (1)	0	0	2 (0.1) 0.0 (2)	0	4 (0.1) 0.0 (5)
Large cell lung cancer Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Lung adenocarcinoma Event rate (e)	1 (0.3) 0.1 (1)	0	1 (0.3) 0.1 (1)	2 (0.1) 0.0 (2)	2 (0.1) 0.1 (2)	6 (0.1) 0.0 (6)
Malignant melanoma Event rate (e)	1 (0.3) 0.1 (1)	1 (0.3) 0.1 (1)	1 (0.3) 0.1 (1)	6 (0.2) 0.1 (6)	1 (0.0) 0.0 (1)	10 (0.2) 0.1 (10)
Myelodysplastic syndrome Event rate (e)	1 (0.3) 0.1 (1)	0	1 (0.3) 0.1 (1)	1 (0.0) 0.0 (1)	1 (0.0) 0.0 (1)	5 (0.1) 0.0 (5)
Oropharyngeal squamous cell carcinoma Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Pancreatic neoplasm Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Papillary renal cell carcinoma Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Plasma cell myeloma Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	3 (0.1) 0.0 (3)
Skin squamous cell carcinoma recurrent Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Squamous cell carcinoma of lung Event rate (e)	1 (0.3) 0.1 (1)	0	0	2 (0.1) 0.0 (2)	0	4 (0.1) 0.0 (4)
Thyroid cancer Event rate (e)	1 (0.3) 0.1 (1)	0	0	1 (0.0) 0.0 (1)	0	1 (0.0) 0.0 (1)
Transitional cell carcinoma Event rate (e)	1 (0.3) 0.1 (1)	2 (0.6) 0.1 (2)	3 (0.8) 0.2 (3)	7 (0.2) 0.1 (8)	4 (0.1) 0.2 (6)	15 (0.3) 0.1 (17)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

"Second primary malignancy" refers to AEs in the narrow SMQs of 'malignant or unspecified tumours' customized to exclude preferred terms of 'congenital fibrosarcoma,' 'congenital malignant neoplasm,' 'congenital retinoblastoma,' 'metastases to…,' 'metastasis,' 'metastatic neoplasm,' 'prostate cancer….' 'carcinoid tumour of the prostate' and 'neoplasm prostate' and (inclusive of) narrow SMQ of 'myelodysplastic syndrome' and (inclusive of) all preferred terms under high level term of 'myeloproliferative disorders (excl leukaemias)'; non-melanoma skin cancers are excluded (preferred terms of 'basal cell carcinoma,' 'basosquamous carcinoma,' 'basosquamous carcinoma of skin,' 'keratoacanthoma,' 'skin cancer,' 'skin cancer metastatic,' 'squamous cell carcinoma,' 'squamous cell carcinoma of skin' and 'lip squamous cell carcinoma').

Time-adjusted rate per 100 patient-years and number of events (e) are shown. Time-adjusted rate per 100 patient-years is calculated as the total number of occurrences of event divided by the total treatment-emergent period for each treatment group times 100. Patients can have more than 1 occurrence of each event. Adverse events that are continuous but change grade are counted as 1 event.

Number of patients (n) reporting at least 1 event of second primary malignancy and percentage of patients (%) are shown. NCI-CTCAE v4.03.

ADT: androgen deprivation therapy; AE: adverse event; CRF: case report form; DB: double-blind; ENZA: enzalutamide; excl: excluding; ISS: Integrated Summary of Safety; max: maximum; min: minimum; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Drug-related TEAEs are TEAEs that were judged by the investigator as possibly, probably or definitely related to study drug.

¶ Second primary malignancy leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

Adverse Drug Reactions

Section 4.8 of the SmPC has been updated to reflect the addition of the EMBARK safety population (N=5110).

Table 54: Adverse Reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	**Adverse reaction and frequency**
Blood and lymphatic system disorders	Uncommon: leucopenia, neutropenia Not known*: thrombocytopenia
Immune system disorders	Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema
Psychiatric disorders	Common: anxiety Uncommon: visual hallucination
Nervous system disorders	Common: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome, cognitive disorder Uncommon: seizure¥ Not known*: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease† Not known*: QT-prolongation (see sections 4.4 and 4.5)
Vascular disorders	Very common: hot flush, hypertension
Gastrointestinal disorders	Not known*: nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common: dry skin, pruritus Not known*: erythema multiforme, rash
Musculoskeletal and connective tissue disorders	Very common: fractures‡ Not known*: myalgia, muscle spasms, muscular weakness, back pain
Reproductive system and breast disorder	Common: gynaecomastia, nipple pain, breast tenderness
General disorders and administration site conditions	Very common: asthenia, fatigue
Injury, poisoning and procedural complications	Very common: fall

* Spontaneous reports from post-marketing experience. ¥ As evaluated by narrow SMQs of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death.† As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery. ‡ Includes all preferred terms with the word 'fracture' in bones.

Laboratory findings

Haematology

Table 55. Haematology Results: Summary of Grade 3 and 4 post-baseline laboratory abnormalities (Safety Groups)

Parameter, Unit [Direction of Criteria], n (%)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 4701)
Hemoglobin (g/L) [low]	2 (0.6)	1 (0.3)	1 (0.3)	75 (2.0)	46 (1.6)	91 (1.9)
Hemoglobin (g/L) [high]	0	0	0	2 (0.1)	1 (0.0)	2 (0.0)
Lymphocytes (10^6/L) [low]	8 (2.3)	9 (2.5)	7 (2.0)	128 (3.4)	91 (3.2)	162 (3.4)
Lymphocytes (10^6/L) [high]	1 (0.3)	1 (0.3)	0	1 (0.0)	1 (0.0)	1 (0.0)
Neutrophils (10^6/L) [low]	2 (0.6)	3 (0.8)	1 (0.3)	35 (0.9)	14 (0.5)	42 (0.9)
Platelets (10^9/L) [low]	0	0	1 (0.3)	10 (0.3)	10 (0.4)	16 (0.3)
Leukocytes (10^9/L) [low]	2 (0.6)	1 (0.3)	0	17 (0.5)	6 (0.2)	20 (0.4)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Grade 3 and 4 toxicities were graded using NCI-CTCAE v4.03.

Number of patients (n) and percentage of patients (%) are shown.

Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients were counted only once for each criterion (high or low), so a single patient could count toward both high and low criteria if the patient had laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period.

The original baseline value was used for patients who received enzalutamide during the DB phase and continued to receive enzalutamide during the OL phase. Baseline value was reset to the last nonmissing measurement at or before the first dose of enzalutamide for patients who received placebo or bicalutamide during the DB phase and crossed over to receive enzalutamide during the OL phase.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Blood Chemistry

Table 56. Blood Chemistry Results: Summary of Grade 3 and 4 post-baseline laboratory abnormalities (Safety Groups)

Parameter (Unit) [Direction of Criteria], n (%)	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 4701)
Alanine aminotransferase (U/L) [high]	3 (0.8)	2 (0.6)	0	18 (0.5)	8 (0.3)	27 (0.6)
Albumin (g/L) [low]	1 (0.3)	1 (0.3)	0	11 (0.3)	6 (0.2)	11 (0.2)
Alkaline phosphatase (U/L) [high]	0	0	2 (0.6)	185 (5.0)	212 (7.5)	203 (4.3)
Aspartate aminotransferase (U/L) [high]	1 (0.3)	2 (0.6)	0	13 (0.3)	13 (0.5)	23 (0.5)
Bilirubin (µmol/L) [high]	0	0	0	3 (0.1)	1 (0.0)	4 (0.1)
Calcium (mmol/L) [low]	0	1 (0.3)	0	19 (0.5)	19 (0.7)	23 (0.5)
Calcium (mmol/L) [high]	1 (0.3)	1 (0.3)	0	5 (0.1)	2 (0.1)	6 (0.1)
Creatinine (µmol/L) [high]	0	0	0	5 (0.1)	8 (0.3)	7 (0.1)
Glucose (mmol/L) [low]	0	0	0	0	0	2 (0.0)
Glucose (mmol/L) [high]	20 (5.7)	33 (9.3)	21 (5.9)	131 (3.5)	114 (4.0)	201 (4.3)
Magnesium (mmol/L) [low]	1 (0.3)	0	0	2 (0.1)	1 (0.0)	3 (0.1)
Magnesium (mmol/L) [high]	0	0	0	5 (0.1)	9 (0.3)	5 (0.1)
Phosphate (mmol/L) [low]	7 (2.0)	0	11 (3.1)	52 (1.4)	24 (0.8)	76 (1.6)
Potassium (mmol/L) [low]	2 (0.6)	4 (1.1)	2 (0.6)	13 (0.3)	17 (0.6)	21 (0.4)
Potassium (mmol/L) [high]	5 (1.4)	4 (1.1)	2 (0.6)	15 (0.4)	12 (0.4)	28 (0.6)
Sodium (mmol/L) [low]	7 (2.0)	3 (0.8)	4 (1.1)	55 (1.5)	38 (1.3)	72 (1.5)
Sodium (mmol/L) [high]	2 (0.6)	0	2 (0.6)	4 (0.1)	2 (0.1)	6 (0.1)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Grade 3 and 4 toxicities were graded using NCI-CTCAE v4.03.

Number of patients (n) and percentage of patients (%) are shown.

Patients were generally counted only once for each parameter. However, for parameters with both high and low criteria, patients were counted only once for each criterion (high or low), so a single patient could count toward both high and low criteria if the patient had laboratory values meeting each criterion. Summaries are based on all test results collected in the treatment-emergent period.

Baseline value is reset to the last nonmissing measurement at or before the first dose of enzalutamide for patients who received placebo or bicalutamide during the DB phase and crossed over to receive enzalutamide during the OL phase. The original baseline value is used for patients who received enzalutamide during the DB phase and continued to receive enzalutamide during the OL phase.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Elevated Liver Function Tests

Table 57. Treatment-Emergent liver function test elevations (Safety Groups)

Parameter Criteria, n (%)	EMBARK DB ENZA+ADT (n = 353)	EMBARK DB PBO+ADT (n = 354)	EMBARK ENZA Mono (n = 354)	Phase 3† DB ENZA+ADT (n = 3728)	Phase 3† DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 4701)
ALT						
n	353	354	354	3727	2828	4699
≥ 3 × ULN	6 (1.7)	10 (2.8)	2 (0.6)	43 (1.2)	45 (1.6)	61 (1.3)
≥ 3 × ULN and worse than baseline	6 (1.7)	10 (2.8)	2 (0.6)	43 (1.2)	45 (1.6)	60 (1.3)
≥ 5 × ULN	3 (0.8)	2 (0.6)	0	18 (0.5)	8 (0.3)	27 (0.6)
≥ 10 × ULN	0	0	0	4 (0.1)	3 (0.1)	9 (0.2)
≥ 20 × ULN	0	0	0	1 (0.0)	0	2 (0.0)
AST						
n	353	354	354	3727	2828	4699
≥ 3 × ULN	3 (0.8)	9 (2.5)	2 (0.6)	50 (1.3)	47 (1.7)	67 (1.4)
≥ 3 × ULN and worse than baseline	3 (0.8)	9 (2.5)	2 (0.6)	50 (1.3)	46 (1.6)	67 (1.4)
≥ 5 × ULN	1 (0.3)	2 (0.6)	0	13 (0.3)	13 (0.5)	23 (0.5)
≥ 10 × ULN	0	0	0	3 (0.1)	2 (0.1)	7 (0.1)
≥ 20 × ULN	0	0	0	0	0	0
ALT or AST						
≥ 3 × ULN	7/353 (2.0)	12/354 (3.4)	4/354 (1.1)	67/3727 (1.8)	66/2828 (2.3)	89/4699 (1.9)
Total bilirubin						
≥ 2 × ULN	0	1/354 (0.3)	1/354 (0.3)	7/3727 (0.2)	3/2828 (0.1)	11/4699 (0.2)
ALP						
≥ 1.5 × ULN	3/353 (0.8)	8/354 (2.3)	10/354 (2.8)	803/3727 (21.5)	729/2828 (25.8)	939/4699 (20.0)
ALT and/or AST and total bilirubin						
ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN	0	0	0	3/3727 (0.1)	1/2828 (0.0)	3/4699 (0.1)
ALT and/or AST and total bilirubin and ALP						
ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN	0	0	0	1/3727 (0.0)	0	1/4699 (0.0)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 30 Sep 2017; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Maximum value on treatment is presented for each liver enzyme and total bilirubin.

Number of patients (n) and percentage of patients (%) are shown. The denominator was the number of patients who had at least 1 nonmissing value during treatment.

Baseline value is reset to the last nonmissing measurement at or before the first dose of enzalutamide for patients who received placebo or bicalutamide during the DB phase and crossed over to receive enzalutamide during the OL phase. The original baseline value is used for patients who received enzalutamide during the DB phase and continued to receive enzalutamide during the OL phase.

ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; ULN: upper limit of normal.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

Vital signs, Physical findings, and other observations related to safety

Table 58. Potentially clinically significant changes in vital signs (Safety Groups)

Parameter (Unit) Direction of Criteria, n/N (%)	EMBARK DB ENZA+ADT (n = 353)	EMBARK DB PBO+ADT (n = 354)	EMBARK ENZA Mono (n = 354)	Phase 3† DB ENZA+ADT (n = 3728)	Phase 3† DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
Systolic blood pressure (mmHg)						
Absolute result ≥ 140§	295/349 (84.5)	287/354 (81.1)	278/354 (78.5)	2519/3710 (67.9)	1837/2807 (65.4)	3867/5059 (76.4)
Absolute result ≥ 180§	37/349 (10.6)	29/354 (8.2)	22/354 (6.2)	288/3710 (7.8)	124/2807 (4.4)	433/5059 (8.6)
Absolute result ≥ 140 and increase from baseline ≥ 20§	160/349 (45.8)	152/354 (42.9)	137/354 (38.7)	1313/3710 (35.4)	730/2807 (26.0)	2034/5059 (40.2)
Absolute result ≥ 180 and increase from baseline ≥ 20§	31/349 (8.9)	26/354 (7.3)	20/354 (5.6)	248/3710 (6.7)	100/2807 (3.6)	374/5059 (7.4)
Absolute result ≥ 180 and increase from baseline ≥ 40§	19/349 (5.4)	17/354 (4.8)	8/354 (2.3)	136/3710 (3.7)	55/2807 (2.0)	209/5059 (4.1)
Absolute result ≤ 90 and decrease from baseline ≥ 30§	5/349 (1.4)	7/354 (2.0)	4/354 (1.1)	33/3710 (0.9)	22/2807 (0.8)	51/5059 (1.0)
Final visit or 2 consecutive visits results ≥ 10 change from baseline	193/349 (55.3)	183/354 (51.7)	160/354 (45.2)	1846/3710 (49.8)	1048/2807 (37.3)	2564/5059 (50.7)
Final visit or 2 consecutive visits results ≥ 15 change from baseline	125/349 (35.8)	125/354 (35.3)	102/354 (28.8)	1269/3710 (34.2)	673/2807 (24.0)	1801/5059 (35.6)
Final visit or 2 consecutive visits results ≥ 20 change from baseline	84/349 (24.1)	82/354 (23.2)	76/354 (21.5)	878/3710 (23.7)	460/2807 (16.4)	1277/5059 (25.2)
Any abnormality	312/349 (89.4)	310/354 (87.6)	299/354 (84.5)	2976/3710 (80.2)	2060/2807 (73.4)	4242/5059 (83.9)
Diastolic blood pressure (mmHg)						
Absolute result ≥ 90§	208/349 (59.6)	182/354 (51.4)	168/354 (47.5)	1530/3710 (41.2)	932/2807 (33.2)	2292/5059 (45.3)
Absolute result ≥ 105§	30/349 (8.6)	18/354 (5.1)	15/354 (4.2)	164/3710 (4.4)	68/2807 (2.4)	244/5059 (4.8)
Absolute result ≥ 90 and increase from baseline ≥ 15§	105/349 (30.1)	81/354 (22.9)	66/354 (18.6)	726/3710 (19.6)	339/2807 (12.1)	1068/5059 (21.1)
Absolute result ≥ 105 and increase from baseline ≥ 15§	28/349 (8.0)	16/354 (4.5)	13/354 (3.7)	131/3710 (3.5)	52/2807 (1.9)	199/5059 (3.9)
Absolute result ≥ 105 and increase from baseline ≥ 30§	5/349 (1.4)	6/354 (1.7)	3/354 (0.8)	41/3710 (1.1)	17/2807 (0.6)	67/5059 (1.3)
Absolute result ≤ 50 and decrease from baseline ≥ 20§	6/349 (1.7)	7/354 (2.0)	9/354 (2.5)	51/3710 (1.4)	32/2807 (1.1)	87/5059 (1.7)
Final visit or 2 consecutive visits results ≥ 5 change from baseline	184/349 (52.7)	193/354 (54.5)	168/354 (47.5)	2035/3710 (54.9)	1203/2807 (42.9)	2757/5059 (54.5)
Final visit or 2 consecutive visits results ≥ 10 change from baseline	122/349 (35.0)	116/354 (32.8)	84/354 (23.7)	1255/3710 (33.8)	689/2807 (24.5)	1708/5059 (33.8)
Final visit or 2 consecutive visits results ≥ 15 change from baseline	58/349 (16.6)	47/354 (13.3)	40/354 (11.3)	571/3710 (15.4)	270/2807 (9.6)	800/5059 (15.8)
Any abnormality	269/349 (77.1)	261/354 (73.7)	240/354 (67.8)	2596/3710 (70.0)	1643/2807 (58.5)	3585/5059 (70.9)
Heart rate (bpm)						
Absolute result ≥ 120 and increase from baseline ≥ 30§	1/349 (0.3)	3/354 (0.8)	1/354 (0.3)	20/3710 (0.5)	18/2807 (0.6)	28/5059 (0.6)
Absolute result ≤ 50 and decrease from baseline ≥ 20§	9/349 (2.6)	16/354 (4.5)	15/354 (4.2)	61/3710 (1.6)	35/2807 (1.2)	105/5059 (2.1)
Any abnormality	10/349 (2.9)	19/354 (5.4)	16/354 (4.5)	80/3710 (2.2)	52/2807 (1.9)	132/5059 (2.6)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) and percentage of patients (%) are shown. The denominator was the number of patients who had at least 1 nonmissing value during treatment.

Baseline value is reset to the last nonmissing measurement at or before the first dose of enzalutamide for patients who received placebo or bicalutamide during the DB phase and crossed over to receive enzalutamide during the OL phase. The original baseline value is used for patients who received enzalutamide during the DB phase and continued to receive enzalutamide during the OL phase.

ADT: androgen deprivation therapy; bpm: beats per minute; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Based on patient's most extreme result value during treatment.

Safety in special populations

Table 59: TEAEs of Grade 3 or higher by subgroups (EMBARK study, Safety Population)

	Enza+LA (N=353)		PBO+LA (N=354)		ENZA (N=354)	
Subgroups	Grade 3/4/5	All	Grade 3/4/5	All	Grade 3/4/5	All
Number of Patients Reporting at Least One TEAE	164 (46.5%)	343 (97.2%)	151 (42.7%)	345 (97.5%)	177 (50.0%)	347 (98.0%)
Study Day Cut Points						
1 - 30 Days	11/353 (3.1%)	199/353 (56.4%)	9/354 (2.5%)	180/354 (50.8%)	11/354 (3.1%)	181/354 (51.1%)
1 - Week 37	65/353 (18.4%)	322/353 (91.2%)	56/354 (15.8%)	316/354 (89.3%)	50/354 (14.1%)	323/354 (91.2%)
> Week 37	129/289 (44.6%)	275/289 (95.2%)	114/311 (36.7%)	288/311 (92.6%)	148/315 (47.0%)	297/315 (94.3%)
Age (Years)						
< 65	21/79 (26.6%)	76/79 (96.2%)	36/90 (40.0%)	89/90 (98.9%)	30/91 (33.0%)	89/91 (97.8%)
>= 65	143/274 (52.2%)	267/274 (97.4%)	115/264 (43.6%)	256/264 (97.0%)	147/263 (55.9%)	258/263 (98.1%)
< 75	119/280 (42.5%)	273/280 (97.5%)	107/267 (40.1%)	262/267 (98.1%)	117/264 (44.3%)	260/264 (98.5%)
>= 75	45/73 (61.6%)	70/73 (95.9%)	44/87 (50.6%)	83/87 (95.4%)	60/90 (66.7%)	87/90 (96.7%)
< 85	163/352 (46.3%)	342/352 (97.2%)	149/349 (42.7%)	340/349 (97.4%)	173/348 (49.7%)	341/348 (98.0%)
>= 85	1/1 (100%)	1/1 (100%)	2/5 (40.0%)	5/5 (100%)	4/6 (66.7%)	6/6 (100%)
Baseline Body Mass Index (Kg/m2)						
< 18.5	0/0	0/0	0/0	0/0	0/1 (0.0%)	1/1 (100%)
18.5 - 24.9	34/70 (48.6%)	66/70 (94.3%)	30/84 (35.7%)	83/84 (98.8%)	27/62 (43.5%)	58/62 (93.5%)
25 - 29.9	83/181 (45.9%)	176/181 (97.2%)	71/161 (44.1%)	155/161 (96.3%)	94/178 (52.8%)	176/178 (98.9%)
>= 30	46/100 (46.0%)	99/100 (99.0%)	49/106 (46.2%)	104/106 (98.1%)	56/112 (50.0%)	111/112 (99.1%)
Geographic Region						
North America	67/143 (46.9%)	142/143 (99.3%)	58/135 (43.0%)	134/135 (99.3%)	64/133 (48.1%)	133/133 (100%)
Europe	59/129 (45.7%)	123/129 (95.3%)	48/127 (37.8%)	122/127 (96.1%)	76/145 (52.4%)	142/145 (97.9%)
Rest of the World	38/81 (46.9%)	78/81 (96.3%)	45/92 (48.9%)	89/92 (96.7%)	37/76 (48.7%)	72/76 (94.7%)
History of Cardiovascular Disease						
Yes	22/42 (52.4%)	41/42 (97.6%)	19/42 (45.2%)	41/42 (97.6%)	27/47 (57.4%)	46/47 (97.9%)
No	142/311 (45.7%)	302/311 (97.1%)	132/312 (42.3%)	304/312 (97.4%)	150/307 (48.9%)	301/307 (98.0%)

The data cut-off date is 31JAN2023.
Note: Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).

Table 60. Treatment-emergent SAEs by subgroups (EMBARK study, Safety Population)

	Enza+LA (N=353)		PBO+LA (N=354)		ENZA (N=354)	
Subgroups	Grade 3/4/5	All	Grade 3/4/5	All	Grade 3/4/5	All
Number of Patients Reporting at Least One Serious TEAE	110 (31.2%)	123 (34.8%)	100 (28.2%)	112 (31.6%)	116 (32.8%)	131 (37.0%)
Study Day Cut Points						
1 - 30 Days	2/353 (0.6%)	3/353 (0.8%)	2/354 (0.6%)	2/354 (0.6%)	1/354 (0.3%)	2/354 (0.6%)
1 - Week 37	27/353 (7.6%)	35/353 (9.9%)	31/354 (8.8%)	35/354 (9.9%)	16/354 (4.5%)	21/354 (5.9%)
> Week 37	93/289 (32.2%)	99/289 (34.3%)	76/311 (24.4%)	85/311 (27.3%)	105/315 (33.3%)	116/315 (36.8%)
Age (Years)						
< 65	10/79 (12.7%)	14/79 (17.7%)	18/90 (20.0%)	19/90 (21.1%)	16/91 (17.6%)	19/91 (20.9%)
>= 65	100/274 (36.5%)	109/274 (39.8%)	82/264 (31.1%)	93/264 (35.2%)	100/263 (38.0%)	112/263 (42.6%)
< 75	75/280 (26.8%)	87/280 (31.1%)	67/267 (25.1%)	76/267 (28.5%)	75/264 (28.4%)	86/264 (32.6%)
>= 75	35/73 (47.9%)	36/73 (49.3%)	33/87 (37.9%)	36/87 (41.4%)	41/90 (45.6%)	45/90 (50.0%)
< 85	110/352 (31.3%)	123/352 (34.9%)	98/349 (28.1%)	110/349 (31.5%)	113/348 (32.5%)	128/348 (36.8%)
>= 85	0/1 (0.0%)	0/1 (0.0%)	2/5 (40.0%)	2/5 (40.0%)	3/6 (50.0%)	3/6 (50.0%)
Baseline Body Mass Index (Kg/m2)						
< 18.5	0/0	0/0	0/0	0/0	0/1 (0.0%)	0/1 (0.0%)
18.5 - 24.9	23/70 (32.9%)	23/70 (32.9%)	17/84 (20.2%)	24/84 (28.6%)	16/62 (25.8%)	17/62 (27.4%)
25 - 29.9	57/181 (31.5%)	67/181 (37.0%)	46/161 (28.6%)	50/161 (31.1%)	62/178 (34.8%)	71/178 (39.9%)
>= 30	30/100 (30.0%)	33/100 (33.0%)	36/106 (34.0%)	37/106 (34.9%)	38/112 (33.9%)	43/112 (38.4%)
Geographic Region						
North America	35/143 (24.5%)	40/143 (28.0%)	37/135 (27.4%)	42/135 (31.1%)	42/133 (31.6%)	46/133 (34.6%)
Europe	45/129 (34.9%)	50/129 (38.8%)	35/127 (27.6%)	40/127 (31.5%)	48/145 (33.1%)	54/145 (37.2%)
Rest of the World	30/81 (37.0%)	33/81 (40.7%)	28/92 (30.4%)	30/92 (32.6%)	26/76 (34.2%)	31/76 (40.8%)
History of Cardiovascular Disease						
Yes	15/42 (35.7%)	16/42 (38.1%)	16/42 (38.1%)	18/42 (42.9%)	21/47 (44.7%)	24/47 (51.1%)
No	95/311 (30.5%)	107/311 (34.4%)	84/312 (26.9%)	94/312 (30.1%)	95/307 (30.9%)	107/307 (34.9%)

The data cut-off date is 31JAN2023.
Note: Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).

Table 61. Treatment-emergent AEs by age group (Safety Groups)

Category	EMBARK			Phase 3†		Total‡
	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	ENZA±ADT (n = 5110)
Age group, n (%)						
< 65 years	79 (22.4)	90 (25.4)	91 (25.7)	805 (21.6)	668 (23.6)	1122 (22.0)
65 to < 75 years	201 (56.9)	177 (50.0)	173 (48.9)	1650 (44.3)	1239 (43.8)	2285 (44.7)
75 to < 85 years	72 (20.4)	82 (23.2)	84 (23.7)	1116 (29.9)	811 (28.7)	1498 (29.3)
≥ 85 years	1 (0.3)	5 (1.4)	6 (1.7)	157 (4.2)	111 (3.9)	205 (4.0)
Patients with any TEAE, n/N (%)						
< 65 years	76/79 (96.2)	89/90 (98.9)	89/91 (97.8)	747/805 (92.8)	606/668 (90.7)	1051/1122 (93.7)
65 to < 75 years	197/201 (98.0)	173/177 (97.7)	171/173 (98.8)	1570/1650 (95.2)	1136/1239 (91.7)	2169/2285 (94.9)
75 to < 85 years	69/72 (95.8)	78/82 (95.1)	81/84 (96.4)	1069/1116 (95.8)	733/811 (90.4)	1430/1498 (95.5)
≥ 85 years	1/1 (100)	5/5 (100)	6/6 (100)	150/157 (95.5)	101/111 (91.0)	198/205 (96.6)
Patients with any serious TEAE, n/N (%)						
< 65 years	14/79 (17.7)	19/90 (21.1)	19/91 (20.9)	216/805 (26.8)	144/668 (21.6)	329/1122 (29.3)
65 to < 75 years	73/201 (36.3)	57/177 (32.2)	67/173 (38.7)	530/1650 (32.1)	331/1239 (26.7)	833/2285 (36.5)
75 to < 85 years	36/72 (50.0)	34/82 (41.5)	42/84 (50.0)	455/1116 (40.8)	262/811 (32.3)	695/1498 (46.4)
≥ 85 years	0/1 (0)	2/5 (40.0)	3/6 (50.0)	76/157 (48.4)	44/111 (39.6)	114/205 (55.6)
Patients with any grade ≥ 3 TEAE, n/N (%)§						
< 65 years	21/79 (26.6)	36/90 (40.0)	30/91 (33.0)	296/805 (36.8)	219/668 (32.8)	450/1122 (40.1)
65 to < 75 years	98/201 (48.8)	71/177 (40.1)	87/173 (50.3)	679/1650 (41.2)	452/1239 (36.5)	1052/2285 (46.0)
75 to < 85 years	44/72 (61.1)	42/82 (51.2)	56/84 (66.7)	552/1116 (49.5)	312/811 (38.5)	822/1498 (54.9)
≥ 85 years	1/1 (100)	2/5 (40.0)	4/6 (66.7)	89/157 (56.7)	51/111 (45.9)	130/205 (63.4)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Number of patients (n) reporting at least 1 event per subgroup and percentage of patients (%) are shown. The N value provided in these age group rows represents the denominator used to calculate the TEAE percentages of the respective age subgroups.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ Grade ≥ 3, based on National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.

Safety related to drug-drug interactions and other interactions

No new data on safety related to drug-drug interactions and other interactions have been provided with this submission.

Discontinuation due to adverse events

Enzalutamide vs placebo in combination with ADT

In the EMBARK enzalutamide plus ADT group, the most frequent (≥ 1%) TEAEs leading to discontinuation of study drug were fatigue (3.4% enzalutamide plus ADT vs. 1.1% placebo plus ADT), hot flush (2.0% vs. 1.1%) and nausea (1.1% vs. 0.3%) (see Table 62).

In the phase 3 enzalutamide plus ADT group, the most frequent (≥ 0.5%) TEAEs leading to discontinuation of study drug were fatigue (1.6% enzalutamide plus ADT vs. 1.1% placebo plus ADT), spinal cord compression (0.9% vs. 0.7%), back pain (0.8% vs. 0.7%), bone pain (0.7% vs. 1.3%), general physical health deterioration (0.6% vs. 0.5%), nausea (0.6% vs. 0.4%) and cancer pain (0.5% vs. 0.3%) (data not shown).

Enzalutamide monotherapy

In the open-label enzalutamide monotherapy group in the EMBARK study, the most frequent (≥ 1%) TEAEs leading to discontinuation of study drug were fatigue (2.3%) and asthenia (1.4%) (see Table 60).

Table 62. Treatment-Emergent Adverse Events leading to study drug discontinuation in at least 0.5% patients in any treatment group by Preferred Term (EMBARK study, Safety Population)

	ENZA + LA (N=353)		PBO + LA (N=354)		ENZA (N=354)	
Preferred Term	All (a)	Per 100 PY (b)	All (a)	Per 100 PY (b)	All (a)	Per 100 PY (b)
Number of Patients Reporting at Least One TEAE(a) / Total Treatment Emergent Period (Patient-Years) (b)	60 (17.0%)	1535.48	32 (9.0%)	1423.11	55 (15.5%)	1571.94
Fatigue	12 (3.4%)	12 (0.8)	4 (1.1%)	4 (0.3)	8 (2.3%)	8 (0.5)
Hot flush	7 (2.0%)	7 (0.5)	4 (1.1%)	4 (0.3)	0 (0.0%)	0 (0.0)
Nausea	4 (1.1%)	4 (0.3)	1 (0.3%)	1 (<0.1)	2 (0.6%)	2 (0.1)
Decreased appetite	3 (0.8%)	3 (0.2)	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (<0.1)
Memory impairment	3 (0.8%)	3 (0.2)	2 (0.6%)	2 (0.1)	1 (0.3%)	1 (<0.1)
Diarrhoea	2 (0.6%)	2 (0.1)	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (<0.1)
Insomnia	2 (0.6%)	2 (0.1)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Pleural effusion	2 (0.6%)	2 (0.1)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Seizure	2 (0.6%)	2 (0.1)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Syncope	2 (0.6%)	2 (0.1)	1 (0.3%)	1 (<0.1)	0 (0.0%)	0 (0.0)
Confusional state	1 (0.3%)	1 (<0.1)	0 (0.0%)	0 (0.0)	3 (0.8%)	3 (0.2)
Death	1 (0.3%)	1 (<0.1)	0 (0.0%)	0 (0.0)	3 (0.8%)	3 (0.2)
Fall	1 (0.3%)	1 (<0.1)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Headache	1 (0.3%)	1 (<0.1)	1 (0.3%)	1 (<0.1)	3 (0.8%)	3 (0.2)
Acute myocardial infarction	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)	0 (0.0%)	0 (0.0)
Asthenia	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (<0.1)	5 (1.4%)	5 (0.3)
Balance disorder	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Cognitive disorder	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Depression	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (<0.1)	3 (0.8%)	3 (0.2)
Gynaecomastia	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Hypertension	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)
Lethargy	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	2 (0.6%)	2 (0.1)

The data cut-off date is 31JAN2023. MedDRA Version: 25.1.
(a) Patients having at least one Treatment Emergent Adverse Event. Patients with multiple events for a given PT are counted only once for the PT. Events are sorted by decreasing frequency of PT in All column in the ENZA+LA group.
(b) Total Treatment Emergent Period in 100 Patient-Years is calculated as the sum of each patient's length of treatment emergent period in days divided by 365.25*100. Time-adjusted rate per 100 patient-year calculated as number of occurrences of event divided by the number of patient-years of treatment emergent surveillance for each treatment group and then times 100. Patients can have more than one occurrence of each event.

Table 63. Treatment-emergent Adverse Events leading to study drug discontinuation in ≥ 2 patients, by Preferred Term (Safety Groups)

	EMBARK			Phase 3†		
Preferred Term (MedDRA v25.1), n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
TEAE leading to study drug discontinuation§	60 (17.0)	32 (9.0)	55 (15.5)	596 (16.0)	437 (15.4)	979 (19.2)
Fatigue	12 (3.4)	4 (1.1)	8 (2.3)	58 (1.6)	31 (1.1)	92 (1.8)
Hot flush	7 (2.0)	4 (1.1)	0	7 (0.2)	4 (0.1)	7 (0.1)
Nausea	4 (1.1)	1 (0.3)	2 (0.6)	23 (0.6)	12 (0.4)	37 (0.7)
Decreased appetite	3 (0.8)	0	1 (0.3)	9 (0.2)	8 (0.3)	16 (0.3)
Memory impairment	3 (0.8)	2 (0.6)	1 (0.3)	7 (0.2)	2 (0.1)	9 (0.2)
Diarrhoea	2 (0.6)	0	1 (0.3)	5 (0.1)	1 (0.0)	8 (0.2)
Insomnia	2 (0.6)	0	0	3 (0.1)	1 (0.0)	3 (0.1)
Pleural effusion	2 (0.6)	0	0	3 (0.1)	1 (0.0)	4 (0.1)
Seizure	2 (0.6)	0	2 (0.6)	8 (0.2)	2 (0.1)	17 (0.3)
Syncope	2 (0.6)	1 (0.3)	0	6 (0.2)	3 (0.1)	8 (0.2)
Acute myocardial infarction	0	2 (0.6)	0	3 (0.1)	3 (0.1)	6 (0.1)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

AE: adverse event; ADT: androgen deprivation therapy; CRF: case report form; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

§ TEAE leading to study drug discontinuation is from AE CRF and includes TEAEs with action taken of permanent discontinuation.

Dose interruptions

Enzalutamide vs placebo in combination with ADT

In the EMBARK enzalutamide plus ADT group, the most frequent (≥ 1%) TEAEs leading to a dose interruption were fatigue (2.8% enzalutamide plus ADT vs. 1.7% placebo plus ADT), hypertension (2.8% vs. 1.1%) and headache (1.1% vs. 0.3%) (see Table 62).

In the phase 3 enzalutamide plus ADT group, the most frequent (≥ 0.5%) TEAEs leading to a dose interruption were: fatigue (1.6% enzalutamide plus ADT vs. 0.6% placebo plus ADT), hypertension (1.0% vs. 0.4%), nausea (1.0% vs. 0.8%), asthenia (0.7% vs. 0.3%), decreased appetite (0.7% vs. 0.5%), vomiting (0.7% vs. 0.5%), pneumonia (0.5% vs. 0.1%) and diarrhea (0.5% vs. 0.4%) (results partially shown in Table 64).

Enzalutamide monotherapy

In the open-label enzalutamide monotherapy group in the EMBARK study, the most frequent (≥ 1%) TEAEs leading to dose interruption were fatigue (4.2%), headache (1.4%) and dizziness, asthenia and weight decreased (1.1% each) (results partially shown in Table 62).

Table 64. Treatment-emergent Adverse Events leading to a dose interruption reported in ≥ 2 patients, by Preferred Term (Safety Groups)

	EMBARK			Phase 3†		
Preferred Term (MedDRA v25.1), n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
TEAE leading to dose interruption of study drug	56 (15.9)	43 (12.1)	66 (18.6)	541 (14.5)	290 (10.3)	829 (16.2)
Fatigue	10 (2.8)	6 (1.7)	15 (4.2)	61 (1.6)	18 (0.6)	104 (2.0)
Hypertension	10 (2.8)	4 (1.1)	3 (0.8)	37 (1.0)	11 (0.4)	54 (1.1)
Headache	4 (1.1)	1 (0.3)	5 (1.4)	15 (0.4)	6 (0.2)	27 (0.5)
Aspartate aminotransferase increased	2 (0.6)	1 (0.3)	1 (0.3)	7 (0.2)	8 (0.3)	12 (0.2)
Back pain	2 (0.6)	0	0	11 (0.3)	6 (0.2)	13 (0.3)
Disturbance in attention	2 (0.6)	0	0	6 (0.2)	1 (0.0)	7 (0.1)
Dizziness	2 (0.6)	2 (0.6)	4 (1.1)	15 (0.4)	8 (0.3)	28 (0.5)
Fall	2 (0.6)	3 (0.8)	1 (0.3)	11 (0.3)	4 (0.1)	17 (0.3)
Hot flush	2 (0.6)	4 (1.1)	1 (0.3)	6 (0.2)	4 (0.1)	7 (0.1)
Nausea	2 (0.6)	1 (0.3)	2 (0.6)	37 (1.0)	22 (0.8)	48 (0.9)
Pneumonia	2 (0.6)	0	0	20 (0.5)	4 (0.1)	29 (0.6)
Pollakiuria	2 (0.6)	0	0	2 (0.1)	0	2 (0.0)
Depression	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.1)	3 (0.1)	5 (0.1)
Diarrhoea	1 (0.3)	2 (0.6)	0	18 (0.5)	11 (0.4)	27 (0.5)
COVID-19	0	2 (0.6)	2 (0.6)	0	2 (0.1)	2 (0.0)
Oedema peripheral	0	2 (0.6)	1 (0.3)	2 (0.1)	5 (0.2)	3 (0.1)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

In EMBARK, most patients who suffered dose interruptions only had one dose interruption (11.6% in enza+ADT, vs. 12.1% in placebo+ADT, vs. 15.5% in enza-mono). In the enza+ADT arm 5.7% of dose interruptions entailed two dose interruptions (vs. 2.8% in placebo+ADT and 2% in enza-mono).

Dose reductions

Enzalutamide vs placebo in combination with ADT

In the EMBARK enzalutamide plus ADT group, the most frequent (≥ 1%) TEAEs leading to a dose reduction were fatigue (2.3% enzalutamide plus ADT vs. 1.4% placebo plus ADT) and hypertension (1.4% vs. 0%) (Table 65).

In the phase 3 enzalutamide plus ADT group, the most frequent (≥ 0.5%) TEAEs leading to a dose reduction were: fatigue (2.1% enzalutamide plus ADT vs. 0.5% placebo plus ADT), asthenia (0.7% vs. 0.1%) and nausea (0.5% vs. 0.2%)(Table 65).

Enzalutamide monotherapy

In the open-label enzalutamide monotherapy group in the EMBARK study, the most frequent (≥ 1%) TEAEs leading to a dose reduction were fatigue (7.9%), asthenia (2.0%) and dizziness and gynecomastia (1.4% each) (results partially shown in Table 65).

Table 65. Treatment-emergent adverse events leading to dose reduction reported in ≥ 2 patients, by Preferred Term (Safety Groups)

	EMBARK			Phase 3†		
Preferred Term (MedDRA v25.1), n (%)	DB ENZA+ADT (n = 353)	DB PBO+ADT (n = 354)	ENZA Mono (n = 354)	DB ENZA+ADT (n = 3728)	DB PBO+ADT (n = 2829)	Total‡ ENZA±ADT (n = 5110)
TEAE leading to dose reduction of study drug	25 (7.1)	16 (4.5)	56 (15.8)	208 (5.6)	67 (2.4)	352 (6.9)
Fatigue	8 (2.3)	5 (1.4)	28 (7.9)	77 (2.1)	14 (0.5)	136 (2.7)
Hypertension	5 (1.4)	0	2 (0.6)	16 (0.4)	1 (0.0)	24 (0.5)
Asthenia	3 (0.8)	1 (0.3)	7 (2.0)	25 (0.7)	4 (0.1)	46 (0.9)
Dizziness	3 (0.8)	0	5 (1.4)	12 (0.3)	4 (0.1)	18 (0.4)
Memory impairment	2 (0.6)	2 (0.6)	0	3 (0.1)	2 (0.1)	3 (0.1)
Nausea	2 (0.6)	0	0	17 (0.5)	5 (0.2)	23 (0.5)
Hot flush	0	3 (0.8)	2 (0.6)	3 (0.1)	3 (0.1)	6 (0.1)

All patients who received at least 1 dose of study drug (enzalutamide, placebo) in their respective phase 3 study or received at least 1 dose of enzalutamide in phase 2 studies. For EMBARK, study drug includes enzalutamide, leuprolide and placebo (Safety Population).

Data cutoff dates were as follows: EMBARK: 31 Jan 2023; PROSPER: 15 Oct 2019; ARCHES: 28 May 2021; AFFIRM: 20 Feb 2018; PREVAIL: 21 Mar 2019; Asian PREVAIL: 04 Nov 2020; TERRAIN: 17 Feb 2018 and STRIVE: 30 May 2018.

Patients with multiple events for a given preferred term were counted only once for each preferred term. Number of patients (n) and percentage of patients (%) are shown. Events are sorted by decreasing frequency of preferred term in the ENZA+ADT group in the EMBARK study.

ADT: androgen deprivation therapy; DB: double-blind; ENZA: enzalutamide; ISS: Integrated Summary of Safety; Mono: monotherapy; OL: open-label; PBO: placebo; SCS: Summary of Clinical Safety; TEAE: treatment-emergent adverse event.

† The phase 3 studies include EMBARK (ENZA+ADT and PBO+ADT arms) and DB phase for PROSPER, ARCHES, AFFIRM, PREVAIL and Asian PREVAIL.

‡ Total enzalutamide summarizes all enzalutamide-treated patients during DB and/or OL periods of EMBARK (ENZA+ADT and ENZA Mono arms), PROSPER, ARCHES, AFFIRM, PREVAIL, Asian PREVAIL, TERRAIN and STRIVE.

In EMBARK, most patients who suffered dose reductions only had one dose reduction (4.8% in enza+ADT, 2.3% in placebo+ADT and 9% in enza-mono). In the enza-mono arm 4.5% of dose reductions entailed two dose reductions (vs. 1.1% in enza+ADT and 1.7% in placebo+ADT).

Post marketing experience

Enzalutamide became commercially available as Xtandi® in the US in Sep 2012. In Europe, enzalutamide was initially approved in Jun 2013, but was made available in France through a temporary authorisation for use in Apr 2013.

The safety profile of enzalutamide is described in the Periodic Safety Update Reports (PSURs) submitted to the regulatory authorities in accordance with the requirements set out in the list of Union reference dates (EURD list).

There was no new significant information received for enzalutamide during the last reporting period that resulted in an impact on the established safety profile or risk characterisation of the safety concerns.

2.5.1. Discussion on clinical safety

The primary safety basis of this submission is the study EMBARK, which included three arms: enzalutamide+ADT (N=353), placebo+ADT (N=354) and enzalutamide monotherapy (N=354). The enza+ADT and placebo+ADT arms were double-blind, whereas enza-mono was open-label. Direct comparisons of enzalutamide monotherapy to other treatment groups have limitations as the enzalutamide monotherapy group was open label.

Safety data are presented in tables including results from the three arms of EMBARK, together with the safety Pool of phase 3 and 2 clinical trials of enzalutamide in patients with mHSPC, nmCRPC or mCRPC (hereinafter "the Pool"). It is noted that the indication sought with this submission refers to earlier stages of the disease, nmSPC, meaning that patients are in overall better health status than patients included in the Pool and that their life expectancy is also supposed to be longer.

Almost all patients in any of the three arms of EMBARK had an TE**AE**: 97.2% in enza+ADT, 97.5% in placebo+ADT, and 98% in enza-mono. When compared with the Pool the percentages in EMBARK are slightly higher (Pool: 94.8% in enza+ADT vs. 91.1% in placebo+ADT), but this could be explained by the notably longer treatment exposure in EMBARK than in the Pool. In the modified treatment-emergent period the difference between percentages was smaller.

The most **frequently reported TEAEs** in EMBARK were in line with the known safety profile for enzalutamide: no new signals were identified. However, it is noted that overall there is a trend towards an increase in the reporting rates for some AEs compared with the Pool, likely due to the higher treatment exposure in EMBARK. Most of the AEs which were increased in EMBARK with respect to the Pool were considered as AESIs and are therefore further discussed in more detail in the subsequent sections of this discussion under their respective section ("fatigue", "fall", "memory impairment", "rash", "hypertension"). The differences observed in "hot flush" (68.8% in enza+ADT in EMBARK vs. 23.1% in enza+ADT in the Pool; 57.3% in placebo+ADT in EMBARK vs. 17% in the Pool) could be due to the patients' baseline characteristics, specifically hormonal status and testosterone levels at study entry. Patients enrolled in the EMBARK study were required to have a serum testosterone level ≥150 ng/dL at screening (physiologic testosterone levels) while most of the studies included in the Pool were performed in the castration-resistant setting so patients needed to be surgically/medically castrated before study entry. The MAH has also provided some publications that justify that hot flushes correlate with drops in serum testosterone, which is quite well understood, and that the absolute levels of plasma sex hormones are less important in the pathophysiology of hot flushes than the dynamic reduction of testosterone levels. This could be quite relevant in this study, where patients suffered from drastic drops of the testosterone levels at the moment of introducing ADT.

Grade ≥3 TEAEs were reported in 46.5% of patients in enza+ADT, 42.7% in placebo+ADT and 50% in enza-mono. The most frequently reported G≥3 TEAEs in enza+ADT were "hypertension" (6.8% in enza+ADT, 5.1% in placebo+ADT, 5.4% in enza-mono), "syncope" (4.2% in enza+ADT, 1.7% in placebo+ADT, 2% in enza-mono) and "fatigue" (3.4% in enza+ADT, 1.4% in placebo+ADT, 4% in enza-mono). The incidences were higher in EMBARK than in the Pool, likely reflecting the longer exposure in EMBARK.

Drug-related TEAEs were reported in 87% of patients in enza+ADT, 80.8% in placebo+ADT and 88.7% in enza-mono. The percentages in EMBARK are overall higher than the percentages reported for the Pool: 66.8% in enza+ADT and 53.9% in placebo+ADT. As said, this could be explained by the longer exposure in EMBARK compared with the Pool. It should be noted that the number of drug-related TEAEs is slightly higher with enzalutamide in monotherapy than with enzalutamide in combination with ADT.

The increase in the rate of drug-related TEAEs in enza-mono in comparison with enza+ADT seems to be driven by the rates of "gynaecomastia", which are relevantly increased in enza-mono vs. enza+ADT or placebo+ADT: 42.9% in enza-mono vs. 6.5% in enza+ADT or 7.9% in placebo+ADT. Without the administration of ADT the levels of serum testosterone are higher than when ADT is administered, and since testosterone is associated with those adverse events, when enzalutamide is administered as monotherapy the occurrence of those AEs increases. A paragraph in section 4.8 of the SmPC reflects this detail. In addition to gynaecomastia, nipple pain (3.1% vs 15.3%), breast tenderness (1.4% vs 14.4%) and ischemic heart disease (5.4% vs 9%) were also more frequently reported in the combination arm than the monotherapy arm, respectively. Considering these differences, nipple pain and breast tenderness were included as ADRs in section 4.8 of the SmPC.

There were other PTs which were increased in the enza-mono arm in comparison with enza+ADT, such as "fatigue": 39.7% in enza+ADT, 28% in placebo+ADT and 44.1% in enza-mono. Conversely, other PTs such as "hot flush" were reported with a lower frequency in enza-mono than in the other two arms: 68.6% in enza+ADT, 55.4% in placebo+ADT and 20.6% in enza-mono. "Hypertension" was also reported

with a slightly lower frequency in enza-mono: 13% in enza+ADT, 8.2% in placebo+ADT and 10.7% in enza-mono. It is noted that "libido decreased" and "erectile dysfunction", which are AEs that can adversely impact on patients' quality of life, are reported with a similar frequency in the three arms; meaning that removing ADT from the treatment does not translate into remarkable improvements in the sexual sphere.

It should be noted that overall it does not seem that the (slightly) increase in the rates of SAEs in the enza-mono arm are driven by any particular PT. Of note, the administration of enzalutamide as monotherapy does not translate into a lower rate of SAEs in comparison with the administration of enzalutamide in combination with leuprolide, in contrast to what would be expected.

The percentage of SAEs in EMBARK is similar to the percentage of SAEs in the Pool; although it is also noted that the difference between the enza+ADT arm and the placebo+ADT arm is subtler in EMBARK (34.8% vs. 31.6%) than in the Pool (34.3% vs. 27.6%). Although patients enrolled in EMBARK were in earlier stages of the disease, it is not surprising that the rate of SAEs was similar to the rate in the Pool considering the longer treatment exposure in EMBARK. The rates per 100 P-Y of "syncope" and "osteoarthritis" were higher in the enza+ADT arm of EMBARK than in the enza+ADT arm of the Pool ("syncope": 0.7 in the enza+ADT arm of EMBARK vs. 0.4 in the enza+ADT arm of the Pool; "osteoarthritis": 0.6 in the enza+ADT arm of EMBARK vs. 0.3 in the enza+ADT arm of the Pool).

In total, there were 33 (9.3%) **deaths** in the enza+ADT arm, vs. 55 (15.5%) in the placebo+ADT arm and 42 (11.9%) in the enza-mono arm. The percentage of deaths is relevantly lower in EMBARK than in the Phase 3 studies, probably due to the fact that patients enrolled in EMBARK were in earlier stages of the disease and therefore their overall health status was better. The main cause of death was disease progression (0.6% in enza+ADT, 0% in placebo+ADT, and 0.3% in enza-mono).

In the enza+ADT arm there were 6 (1.7%) patients with ≥ 1 TEAE resulting in death; while in the placebo+ADT arm there were 3 (0.8%) patients, and in the enza-mono arm there were 8 (2.3%) patients. When time-adjusted, overall TEAE leading to death rate per 100 P-Y was 0.4 in the enza+ADT arm, 0.2 in the placebo+ADT arm, and 0.5 in the enza-mono arm. It is noteworthy to mention that both the number of total deaths and TEAEs leading to death were slightly higher in the enza-mono arm than in the enza+ADT arm or in the placebo+ADT.

The narratives of the three deaths with unknown cause in the enza-mono arm provide very scarce data and it is agreed that no conclusion can be drawn on the cause of death of those subjects. It should be noted that all those subjects had a medical history including arterial hypertension and/or other cardiac conditions; and therefore a cardiac cause of death cannot be discarded. None of the TEAEs leading to death, in any arm, was considered as treatment-related; and this is agreed. However, it should be noted that the potential contribution of enzalutamide to the cardiac deaths cannot be ruled out; although the existence of several confounding factors (i.e. relevant medical history of prior cardiac conditions) is also acknowledged.

TEAEs of special interest (**AESIs**) were selected based on previously recognised risks and/or feedback from regulatory authorities. Regarding the comparison between enza+ADT and enza-mono, it should be noted that "ischemic heart disease" was increased in enza-mono: 9% in enza-mono vs. 5.4% in enza+ADT vs. 5.6% in placebo+ADT. Of those events, 1.4% in enza+ADT were considered as drug-related, vs. 2.3% in enza-mono. In section 4.8 of the SmPC a paragraph describing this selected adverse reaction is already included, and the information has been updated to include these data, since the risk in patients receiving enzalutamide as monotherapy could be higher than the risk in patients receiving enzalutamide in combination with ADT. In section 4.4 of the SmPC, ''malignant melanoma'' was included as one of the most frequently second primary malignancies reported in patients treated with enzalutamide (0.2%).

Similarly, the frequency of "fatigue" was higher in enza-mono than in enza+ADT: 54% in enza-mono vs. 50.4% in enza+ADT vs. 37.9% in placebo+ADT. Of those events, in enza-mono 50.3% were considered as drug-related, vs. 46.2% in enza+ADT. Although the percentage of patients who discontinued treatment due this AE in enza-mono was similar to the percentage of patients in enza+ADT, it is noted that the rates of dose reductions were three times higher in enza-mono than in enza+ADT; as further discussed below.

Conversely, some PTs were reported with lower frequency in enza-mono than in enza+ADT: "hypertension", (21.8% in enza-mono vs. 25.2% in enza+ADT vs. 20.9% in placebo+ADT), "fall" (15.8% in enza-mono vs. 21% in enza+ADT vs. 14.4% in placebo+ADT) and "fracture" (11% in enza-mono vs. 18.4% in enza+ADT vs. 13.6% in placebo+ADT).

No cases of "interstitial lung disease" were reported in EMBARK.

Regarding the comparison between EMBARK and the Pool, some PTs were increased in EMBARK compared with the Pool: "hypertension" (25.2% in the EMBARK's enza+ADT arm vs. 14% in the Pool's enza+ADT arm), "cognitive and memory impairment" (15% in the EMBARK's enza+ADT arm vs. 6.4% in the Pool's enza+ADT arm), "fatigue" (50.4% in the EMBARK's enza+ADT arm vs. 43.1% in the Pool's enza+ADT arm), "fall" (21% in the EMBARK's enza+ADT arm vs. 11.5% in the Pool's enza+ADT arm) and "fracture" (18.4% in the EMBARK's enza+ADT arm vs. 12.3% in the Pool's enza+ADT arm). However, when time-adjusted, the rates were lower in EMBARK than in the Pool: "hypertension" (100 PY rate in EMBARK: 6.6 vs. 7.7 in the Pool), "fatigue" (16.1 in EMBARK vs. 26.4 in the Pool), "fall" (6.8 in EMBARK vs. 7.5 in the Pool), "fracture" (5.7 in EMBARK vs. 8.1 in the Pool). The only exception was "cognitive and memory impairment", which was slightly higher in EMBARK than in the Pool: 100 PY rate in EMBARK: 4.1 vs. 3.6 in the Pool. Taking all this into account, it can be considered that the safety profile of enzalutamide in EMBARK was similar to the already known safety profile of enzalutamide.

When compared with the modified treatment-emergent period the trends are similar or slightly lower than in the total treatment-emergent period; suggesting that the treatment suspension does not translate into a dramatically lower frequency of AESIs. It should be noted, though, that the incidence of musculoskeletal events seems to be notably decreased in the modified treatment-emergent period: in the total treatment-emergent period the incidence was 46.2% in the enza+ADT arm, vs. 41.8% in placebo+ADT, vs. 44.6% in enza-mono; while in the modified treatment-emergent period the incidence was 35.7% in the enza+ADT arm, vs. 37% in placebo+ADT arm, vs. 38.7% in enza-mono. This suggests that the burden associated with those events could be diminished in patients who suspend treatment.

Regarding **laboratory findings**, overall no relevant G3-4 laboratory abnormalities were identified. In terms of haematology the most altered parameter was "low lymphocytes". However, similar frequencies were observed in the three arms (2.3% in enza+ADT, 2.5% in placebo+ADT, 2% in enza-mono), as well as in the Pool (3.4% in enza+ADT and 3.2% in placebo+ADT). All the other haematology G3-4 post-baseline laboratory abnormalities were reported with frequencies lower than 1%.

Regarding blood chemistry parameters, the most altered one was "high glucose" in the three arms: G3-4 abnormalities were reported in 5.7% in enza+ADT, 9.3% in placebo+ADT and 5.9% in enza-mono. In the Pool these findings were similar: 3.5% in enza+ADT vs. 4% in enza-mono. It should be noted that this parameter was more altered in the placebo+ADT arm than in the enza+ADT arm in both EMBARK and the Pool; suggesting there is no particular association with enzalutamide.

Regarding treatment-emergent liver function test elevations, it should be noted that parameters were overall more altered in the placebo+ADT arm than in the enza+ADT or enza-mono arm, suggesting that the observed alterations are not associated with the administration of enzalutamide. The only alteration which was reported with a higher frequency in the enza-mono arm was ALP ≥ 1.5 x ULN: 0.8% in enza+ADT, 2.3% in placebo+ADT and 2.8% in enza-mono. No patients met Hy's law criteria.

In terms of **safety in special populations**, the MAH has provided subgroup analyses by time on treatment, by age, by BMI, by geographic region and by history of cardiovascular disease. It is noted that the MAH has not provided subgroup analyses by race; although considering the low number of patients belonging to races other than White, this is acceptable.

No relevant differences were observed among subgroups. However, it is noted that patients with history of cardiovascular disease seem to be more prone to have G≥3 TEAEs and SAEs than patients without a history of cardiovascular disease. Additionally, it seems that the frequency of G≥3 AEs and SAEs increases as patients are older, which was expectable. Patients older than 85 years old were so scarcely represented in EMBARK that no conclusions can be drawn from that subgroup of patients. In this regard, it is also noted that no relevant differences were observed between enza+ADT and enza-mono; suggesting that the tolerability of the different subgroups of age is similar in both arms.

Most patients who suffered dose reductions only had one dose reduction (4.8% in enza+ADT, 2.3% in placebo+ADT and 9% in enza-mono), although in the enza-mono arm 4.5% of dose reductions entailed two dose reductions (vs. 1.1% in enza+ADT and 1.7% in placebo+ADT). It should be noted that the frequency of TEAEs leading to dose reductions in the Pool was lower than in EMBARK: 5.6% in the enza+ADT arm and 2.4% in the placebo+ADT arm.

The differences in the percentage of TEAEs leading to dose discontinuations between the enza+ADT and placebo+ADT arms seem to be higher in EMBARK than in the Pool (17% vs. 9% in EMBARK; 16% vs. 15.4% in the Pool), which is not surprising considering the higher treatment exposure in EMBARK compared with the Pool. The differences between the enza+ADT arm and placebo+ADT arm in terms of dose interruptions and dose reductions seem to be similar to the differences between arms in the Pool.

The frequency of TEAEs leading to dose interruptions and dose reductions is higher in the enza-mono arm than in the enza+ADT arm although toxicity seems to be managed by dose interruptions and dose reductions, leading to a lower rate of treatment discontinuations. These findings, added to the fact that in the enza-mono arm it was also observed a (slightly) higher rate of SAEs, AEs leading to death, G≥3 TEAEs, drug-related TEAEs, and some AESIs such as "ischemic heart disease". The differences in the TEAE profile between enzalutamide plus ADT and enzalutamide monotherapy appears to be mostly related to the different effect on the levels of testosterone (and oestrogen levels, not shown for this study) expressed through higher incidences of gynecomastia and other related events. Based on the available information and considering also the observed efficacy results, enzalutamide monotherapy can be an alternative treatment option for patients for whom ADT treatment may have some relevant risks, acknowledging that it might not be the most effective option in this setting and that the use of enza as monotherapy may involve an increase in other adverse events. Considering all the above (i.e. the lower efficacy of enzalutamide as monotherapy and the differences in the safety profile), a warning in section 4.4 have been introduced to advise healthcare professionals.

As previously discussed in the efficacy section, in the context of non-metastatic setting and relatively younger and healthier patient population with longer life expectancy than in metastatic setting some of the enzalutamide ADRs including cognitive and memory impairment, seizure, fracture risk and secondary primary malignancy, despite similar or lower incidence, have other clinical significance and on long run may impact the patients' quality of life, which should be taken into consideration. Other potential problem is the cross-resistance between the novel hormonal therapies (NHTs) observed in the RCTs on sequential treatment in metastatic PCa that would limit the treatment possibilities in case of progress to metastatic setting. These aspects could be partially answered by the current study with submission of final OS data (REC).

2.5.2. Conclusions on clinical safety

The safety profile of enzalutamide in combination with ADTin patients with nmCSPC with high-risk BCR was consistent with the established safety profile in other prostate cancer indications and no new safety concerns were identified.

With regard to enzalutamide monotherapy, some ADRs, such as gynecomastia or nipple pain, can have a great impact on the patients' lives and a higher risk of "ischemic heart disease" has also been observed. This should be taken into consideration when deciding to initiate treatment with enzalutamide as monotherapy rather than in combination with ADT, a warning has been included in section 4.4 to advise healthcare professionals.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted RMP version 18 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18 is acceptable.

Safety concerns

Table 66. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischaemic Heart Disease
Important potential risks	None
Missing information	None

Pharmacovigilance plan

To be updated.

Risk minimisation measures

Table 67. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Seizure	Routine risk communication: • SmPC sections 4.4, 4.7, 4.8, and 4.9; • PL sections 2 and 4;	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

	• Recommendation that the decision to continue treatment in patients who develop seizure should be taken case by case, is provided in SmPC Section 4.4 and PL sections 2 and 4; • Concomitant medications associated with higher risk of seizure are described in PL Section 2. Additional risk minimisation measures: • None	• None. Additional pharmacovigilance activities: • None.
Fall	Routine risk communication: • SmPC Section 4.8; • PL Section 4. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fall TDQ for spontaneous reports; • Safety analyses of events of fall in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None.
Non-pathological fracture	Routine risk communication: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fracture TDQ for spontaneous reports; • Safety analyses of events of fracture in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None
Ischemic heart disease	Routine risk communication: • SmPC Section 4.8;	Routine pharmacovigilance activities beyond adverse reactions reporting and signal

	• PL Section 4. Additional risk minimisation measures: • None.	detection: • Safety analyses of events of ischemic heart disease in CSRs of individual enzalutamide clinical trials. Additional pharmacovigilance activities: • None

2.7. *Conclusion*

The CHMP considers that the risk management plan version 18 is acceptable.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xtandi. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Xtandi is indicated as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy.

To be considered "high risk", patients need to present a PSADT ≤9 months and screening PSA of ≥1 ng/mL for patients with prior radical prostatectomy or, at least, 2 ng/mL above the nadir for patients who had prior primary radiotherapy only.

3.1.2. Available therapies and unmet medical need

There are not specific treatments authorized for high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer patients. Management is not uniformly established and the need for immediate treatment in this setting remains controversial and it is often reserved for patients at high risk

of developing symptomatic metastatic disease based on different criteria. Definitive local therapy is the preferred option for high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer patients and for those patients not eligible for local therapy, ADT is often an alternative choice (Marhold M, et all. Cancer Lett. 2022)

3.1.3. Main clinical studies

The efficacy data in support of this application is based on the results from Study MDV3100-13 (EMBARK), a phase 3, randomized study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk non-metastatic prostate cancer progressing (biochemical recurrence) after definitive therapy.

All patients needed to present a baseline PSADT ≤9 months and screening PSA of ≥1 ng/mL for patients with prior radical prostatectomy or, at least, 2 ng/mL above the nadir for patients who had prior primary radiotherapy only.

A total of 1068 patients were randomised to receive enzalutamide plus ADT (n=335), placebo plus ADT (n=358) or enzalutamide as monotherapy (n=355). Enzalutamide was administered as single daily dose of 160 mg (four 40 mg soft capsules).

The primary endpoint of the study was MFS in patients randomised to receive enzalutamide plus ADT compared to patients randomised to receive placebo plus ADT. Key secondary endpoint were MFS in patients randomised to receive enzalutamide as monotherapy compared to patients randomised to receive placebo plus ADT, PSA progression, time to first use of antineoplastic therapy and overall survival.

3.2. Favourable effects

Based on a data cut-off of 31-Jan-2023, the final analysis of MFS, showed an improvement for enzalutamide + ADT in comparison with ADT, with a HR of 0.424 (95% CI: 0.296, 0.607); 2-sided stratified log-rank test P <0.0001 and a median follow-up of around 60 months. A benefit, also in terms of MFS, was shown for enzalutamide monotherapy compared to ADT, HR was 0.631 (95% CI: 0.456, 0.871); 2-sided stratified log-rank test P =0.0049. Several sensitivity analyses confirmed these results.

Other key secondary endpoints showed consistent results with the primary analysis. Treatment with enzalutamide+ADT delayed time to PSA progression (HR 0.068; 95% CI: 0.033, 0.141) and time to first use of new antineoplastic therapy (HR 0.358; 95% CI: 0.263, 0.488). For the enzalutamide monotherapy comparison, a reduction of the risk of PSA progression was also observed (HR 0.331; 95% CI: 0.226, 0.486) and the same for time to first use of new antineoplastic therapy (HR 0.540; 95% CI: 0.411, 0.709).

At the time of the IA OS data was still immature with 130 events out of 271 planned for the Final Analysis. For the enzalutamide + ADT in comparison with ADT OS HR was 0.589 (95% CI: 0.382, 0.908) p = 0.0153 and the pre-specified efficacy boundary (P ≤0.0001) was not crossed at this interim OS analysis. For the enzalutamide monotherapy arm, OS IA results showed an HR 0.782; 95% CI: 0.523, 1.170.

Other secondary efficacy endpoints, including PFS2 (exploratory endpoint), also favoured the enzalutamide+ADT arm and the enzalutamide monotherapy arm, compared to ADT.

The proportion of patients with undetectable PSA at 36 weeks on study treatment was 97.3% in the enzalutamide + ADT group, 71.4% in the placebo + ADT group, and 90.2% in the enzalutamide monotherapy group. The proportion of patients that remained treatment free 2 years after suspension of

treatment was of 34.6% in the enzalutamide + ADT group vs 27.1% in the ADT group and 14.1% in the enzalutamide monotherapy arm.

3.3. Uncertainties and limitations about favourable effects

Overall survival data is still limited with the results from the pre-planned IA being immature. Although a positive trend has been observed and a detrimental effect appears unlikely, the effect of enzalutamide on OS is uncertain. Further OS data are expected to be submitted as soon as available (REC).

3.4. Unfavourable effects

The most frequently reported AEs were in line with the known safety profile for enzalutamide. The most commonly reported AEs in the enza+ADT compared with the placebo+ADT and enza-mono were fatigue (42.8% vs. 12.3% vs. 32.8%), arthralgia (27.5% vs. 7.1% vs. 21.2%), hypertension (23.2% vs. 6.1% vs 19.5%) and fall (21% vs. 6.8% vs. 14.4%).

Grade ≥3 TEAEs were reported in 46.5% of patients in enza+ADT, 42.7% in placebo+ADT and 50% in enza-mono. The most frequently reported G≥3 TEAEs in enza+ADT were "hypertension" (6.8% in enza+ADT, 5.1% in placebo+ADT, 5.4% in enza-mono), "syncope" (4.2% in enza+ADT, 1.7% in placebo+ADT, 2% in enza-mono) and "fatigue" (3.4% in enza+ADT, 1.4% in placebo+ADT, 4% in enza-mono).

Drug-related TEAEs were reported in 87% of patients in enza+ADT, 80.8% in placebo+ADT and 88.7% in enza-mono.

SAEs were reported in 34.8% of patients in the enza+ADT arm, in 31.6% in the placebo+ADT arm and in 37% in the enza-mono arm. The most frequent PTs in the enza+ADT arm were "syncope" (2.5%), and "haematuria", "osteoarthritis" and "pneumonia" (2.3%). In the enza-mono arm the most frequently reported PTs were "haematuria" and "coronary artery disease" (2.3% each), together with "sepsis" (1.7%).

TEAEs leading to death were reported in 6 (1.7%) patients in the enza+ADT arm, in 3 (0.8%) patients in the placebo+ADT arm, and in 8 (2.3%) patients in the enza-mono arm. None of the TEAEs leading to death, in any arm, was considered as treatment-related.

The rate of TEAEs leading to discontinuation was higher in the enza+ADT arm (17%) and in the enza-mono (15.5%) than in the placebo arm (9%). The most frequently reported TEAE leading to discontinuation was "fatigue" in the three arms (3.4% in enza+ADT, 1.1% in placebo+ADT and 2.3% in enza-mono). TEAEs leading to dose interruptions were reported with a frequency of 15.9% in the enza+ADT arm, 12.1% in the placebo+ADT arm and 18.6% in the enza-mono arm. TEAEs leading to dose reductions were more frequent in the enza-mono arm (15.8%) than in the enza+ADT arm (7.1%) or than in the placebo+ADT arm (4.5%). The most frequently reported PT leading to dose reductions was "fatigue": 7.9% in the enza-mono arm vs. 2.3% in the enza+ADT arm and 1.4% in the placebo+ADT arm.

Regarding enzalutamide as monotherapy, an increase in SAEs, AEs leading to death, G≥3 TEAEs, drug-related TEAEs, TEAEs leading to dose reductions/interruptions, and some AESIs such as "ischemic heart disease" was observed. Besides, the administration of enzalutamide as monotherapy entails and increase in other TEAEs, such as gynaecomastia and nipple pain, that can have a great impact on the patients' lives. All ADRs are reflected in SmPC section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable

3.6. Effects Table

Table 68. Effects Table for Xtandi in nmHSPC (data cut-off: 31 Jan 2023)

Effect	Short description	Unit	Treatment Enza+ADT (N= 355)	Control Placebo+ADT (358)	Treatment Enza-Mono (N=355)	Uncertainties / Strength of evidence	References
Favourable Effects							
MFS	Metastasis free survival	Median mo (95% CI)	NR (NR, NR)	NR (85.1 , NR)	NR (NR, NR)		Primary CSR and ECS
		Number of events (%)	45 (12.7)	92 (25.7)	63(17.7)		
		Hazard ratio relative to Placebo plus ADT (95% CI)[a]	0.42 (0.30, 0.61); p < 0.0001		0.63 (0.46, 0.87); p = 0.0049		
Time to PSA progression		Median mo (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)		
		Number of events (%)	8 (2.3)	93 (26.0)	37 (10.4)		
		Hazard ratio relative to Placebo plus ADT (95% CI[a]	0.068 (0.033, 0.141); p < 0.0001		0.33 (0.226, 0.486) p < 0.0001		
Time to first use of antineoplastic therapy		Median mo (95% CI)	NR (NR, NR)	76.2 (71.3, NR)	NR (NR, NR)		
		Number of events (%)	58 (16.3)	140 (39.1)	84 (23.7)		
		Hazard ratio relative to Placebo plus ADT (95% CI)[a]	0.358 (0.263,0.488); p < 0.0001		0.54 (0.41, 0.71); p < 0.0001		
OS	Overall Survival	Median mo (95% CI)	NR	NR	NR	Immaturity of data	
		Number of events (%)	33 (9.3)	55 (15.4)	42 (11.8)		

Effect	Short description	Unit	Treatment Enza+ADT (N= 355)	Control Placebo+ADT (358)	Treatment Enza-Mono (N=355)	Uncertainties / Strength of evidence	References
		Hazard ratio relative to Placebo plus ADT (95% CI)[a]	0.59 (0.38, 0.91) p = 0.0153[b]		0.78 (0.52, 1.17) p = 0.2304[b]		
Unfavourable Effects							
AEs G⩾ 3	Drug related	%	46.5 (17.6)	42.7 (8.8)	50 (16.1)		Primary CSR and SCS
SAEs	All causality (drug-related)	%	34.8 (7.4)	31.6 (2.3)	37 (4.8)		
TEAEs leading to death	All causality (drug-related)	%	1.7 (0)	0.8 (0)	2.3 (0)		
Ischemic heart disease	AE of special interest All causality (drug-related)	%	5.4 (1.4)	5.6 (1.7)	9 (2.3)		

Abbreviations: NR: not reached
Notes: a) prior hormonal therapy. b) The result did not meet the pre-specified two-sided significance level of p ⩽ 0.0001.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results from the EMBARK trial has shown a clear benefit, in terms of MFS, for the combination of enzalutamide + ADT in patients with high risk BCR nmHSPC who are unsuitable for salvage radiotherapy, compared to ADT alone. Of note, a delay in the development of metastatic disease was previously considered of clinical benefit for patients in the nmCRPC setting. These results have been confirmed by several secondary endpoints and sensitivity analyses. Positive results have also been reported for enzalutamide monotherapy in comparison with ADT.

OS data were still immature at the time of the IA and did not reach statistical significance. While a detrimental effect seems unlikely, updated efficacy data are recommended to be submitted to better characterise the efficacy of enzalutamide+ADT and particularly for the enzalutamide monotherapy in this setting.

For enzalutamide monotherapy OS results did not show the same positivity trend as for the combination treatment. This is of particular importance in this early disease setting where a low number of patients receive subsequent therapies and the impact of enzalutamide on the future course of the disease is unknown.

The study has shown that a management approach consisting of suspension of treatment after 36 weeks when PSA values are undetectable could be a valid treatment option as long as a PSA threshold to resume treatment when needed is established (See SmPC section 4.2). While it is not possible to (clearly)

ascertain whether this strategy may have an impact on the efficacy as compared to a continuous administration, positive efficacy results, despite treatment suspension, have been observed.

The safety profile of enzalutamide in combination with ADT is highly consistent with the established safety profile of enzalutamide in combination with ADT in other prostate cancer indications. No new signals were identified. It is nevertheless noted that the clinical setting for the sought indication is not the same as the clinical settings of the already approved prostate cancer indications, which are (mostly) focused on latter stages of the disease. All this considered, the unfavourable effects of enzalutamide in combination with ADT are considered acceptable and are overall clinically manageable.

The safety profile of enzalutamide as monotherapy appears worse than expected, and to some extent even worse than enzalutamide in combination with ADT. Although it is acknowledged that the frequency of some ADR is lower in the monotherapy arm, an increase in some ADR, such as gynaecomastia, nipple pain, and ischemic heart disease, is observed with enzalutamide as monotherapy and reported in section 4.8 of the SmPC.

The B/R of enzalutamide for the treatment of high risk biochemical recurrent nmHSPC is considered positive in combination with ADT and as monotherapy. However, considering the remaining uncertainties with regards to the use of enzalutamide as monotherapy (lower efficacy and no clear OS benefit at this stage), enzalutamide in combination with an LHRH analogue may be a preferred option over enzalutamide alone, leaving the latter to those patients in whom administration of ADT is considered to pose an unacceptable risk. A warning is included in section 4.4. of the SmPC.

3.7.2. Balance of benefits and risks

Based on the efficacy results reported in the EMBARK study, enzalutamide, as monotherapy, or in combination with ADT has shown a clinically relevant benefit over ADT alone in patients with high risk BCR nmHSPC. Even though there are uncertainties on the magnitude of the benefit in terms of OS, especially for with regard to the clinical impact of introducing enzalutamide treatment in this early, the results are considered clinically relevant.

Overall, the risks of enzalutamide in combination with ADT are considered acceptable and are overall clinically manageable. Enzalutamide monotherapy might have a different toxicity profile with some ADRs which could have a relevant impact on patients' lives.

Overall, the benefit/risk of enzalutamide +/- LHRH analogue for the treatment of patients with non-metastatic prostate cancer with high risk BCR for which salvage therapy is not suitable is positive.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Xtandi is positive as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Xtandi to include treatment as monotherapy or in combination with androgen deprivation therapy of adult men with high risk biochemical recurrent (BCR) non-metastatic hormone sensitive prostate cancer (nmHSPC) who are unsuitable for salvage radiotherapy, based on final results from study MDV3100-13 (EMBARK); this is a phase 3, randomized, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy, and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 18 is approved. In addition, the MAH took the opportunity to introduce minor changes to the PI and to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.