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A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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ABSTRACT

Introduction There are limited data from controlled clinical trials of treatments for men with biochemical recurrence (BCR) after definitive therapy for prostate cancer. These nonmetastatic castration-sensitive prostate cancer (CSPC) patients, especially those with high-risk features, often receive androgen deprivation therapy (ADT) prior to metastases, although no consensus on optimal ADT timing exists. ADT plus novel hormonal agents improves survival in metastatic CSPC. The main objective of EMBARK is to assess whether enzalutamide plus luteinizing hormone–releasing hormone agonist (LHRHa) or enzalutamide monotherapy improves metastasis-free survival (MFS) versus monotherapy LHRHa in high-risk nonmetastatic CSPC patients with BCR after definitive therapy.

Methods and analysis EMBARK is a randomised phase 3 study of high-risk nonmetastatic CSPC patients with a PSADT of ≤9 months, and screening PSA of ≥2 ng/mL above the nadir after radiotherapy or ≥1 ng/mL after radical prostatectomy (RP) with or without postoperative radiotherapy. Men were randomised 1:1:1 to enzalutamide 160 mg/day plus LHRHa, placebo plus LHRHa, or enzalutamide monotherapy. Treatment will be suspended at week 37 if patient PSA levels are <0.2 ng/mL and reinstated if levels increase to ≥2.0 ng/mL with RP or ≥5.0 ng/mL without RP. Patients with PSA ≥0.2 ng/mL at week 37 continue until treatment discontinuation criteria are met. The primary endpoint is MFS comparing enzalutamide plus LHRHa versus placebo plus LHRHa. Secondary endpoints are MFS comparing enzalutamide monotherapy versus placebo plus LHRHa, time to PSA progression, time to first use of new antineoplastic therapy, quality of life, and overall survival. Progression-free survival on

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first subsequent therapy is an exploratory endpoint. A total of 1068 study subjects were randomised.

Ethics and dissemination EMBARK follows principles of the World Medical Association Declaration of Helsinki and International Council for Harmonisation Guidelines. Results will be disseminated through research conferences and published articles in peer-reviewed journals.

Trial registration number: NCT02319837

Strengths and limitations of this study

- EMBARK is designed to address the use of enzalutamide early in the prostate cancer disease continuum. It is the first study to determine whether combined therapy with enzalutamide plus luteinizing hormone–releasing hormone agonist (LHRHa) or enzalutamide monotherapy is more effective than placebo plus LHRHa earlier in patients with high-risk nmCSPC.
- A PSA doubling time of ≤9 months is included as a critical inclusion criterion based on its prior demonstration as a significant risk factor for prostate cancer-specific mortality and the primary endpoint of metastasis-free survival is a documented surrogate for overall survival for patients with localised prostate cancer.
- A key feature of this protocol is monitoring PSA levels to suspend treatment in participants with undetectable PSA, while continuing study treatment for those with detectable PSA, to test whether intermittent androgen deprivation or an intermittent androgen treatment holiday allows for clinical benefit along with modest improvements in quality of life.
- A limitation of this study is absence of biomarker analysis for study of enzalutamide response and resistance mechanisms.
- A study limitation is that some patients may develop nonmetastatic castration resistant prostate cancer (nmCRPC) before radiographic progression, based on prior PSA rise, and drop out of the study.

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INTRODUCTION

Background

Approximately one-third of patients experience biochemical recurrence (BCR; ie, prostate-specific antigen [PSA]-only recurrence) within 10 years after primary definitive therapy for prostate cancer.[1–5] The rise in PSA represents prostate cancer recurrence, as well as the likely presence of micrometastatic disease and an increased risk of prostate cancer–related morbidity and mortality.[6] Patients with PSA doubling time (PSADT) <9 months are at high risk for rapidly progressing to radiologically evident metastases and eventual death.[7–9]

There are limited treatments for patients with high-risk nonmetastatic castration-sensitive prostate cancer (nmCSPC) with evidence of disease recurrence by PSA but without overt metastases. Standard of care options include systemic treatment with androgen deprivation therapy (ADT; orchiectomy or luteinizing hormone–releasing hormone agonist [LHRHa] or LHRH antagonist), salvage local therapy, usually with radiotherapy (RT), or observation.[6] For these patients, there is no general clinical consensus on optimal ADT timing either with early treatment to delay progression and hopefully prolong survival or with later treatment once metastases and symptoms develop to lessen the risk of side effects.[10] Given limited data that early ADT may delay progression to metastases in high-risk patients exhibiting high-grade disease (eg, Gleason score of 8–10 or serum PSADT of <12 months),[11] this approach is commonly employed for high-risk men. For patients who have exhausted local treatment options, a recent guideline from the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and Society for Urologic Oncology recommends against

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routinely initiating ADT and using it as intermittent therapy if initiated. Guideline recommendations also call for observation or clinical trial enrollment.[12]

Another option instead of continuous ADT is the use of continuous versus intermittent androgen blockade (IAD), although the latter is considered noninferior to continuous ADT while offering modest quality-of-life (QoL) improvements in patients with (nmCSPC).[13] Finally, there is no general consensus for the use of ADT alone versus ADT plus an antiandrogen (bicalutamide, flutamide, and nilutamide), known as combined androgen blockade (CAB), in patients with nmCSPC. American Society of Clinical Oncology (ASCO) guidelines suggest that CAB be considered in this setting, with personalized patient/physician treatment decisions in light of potential side effects and associated cost concerns.[14]

In an open-label, single-arm phase 2 study of patients with nmCSPC and metastatic CSPC (mCSPC), treatment with enzalutamide monotherapy has been demonstrated to lead to a rapid and durable response, with 92.5% of patients having a PSA decline of ≥80% at 25 weeks.[15] PSA response was maintained with a favorable tumor response and well tolerated at subsequent 1-,[16] 2-,[16] and 3-year[17] open-label follow-ups. While promising, no phase 3 study has yet tested enzalutamide monotherapy. Given data that ADT and novel hormonal agents improve survival and/or radiographic progression–free survival in men with mCSPC, there is a desire to further test such a combination even earlier in the disease course in a Phase 3 study.[18–20]

Rationale

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EMBARK is designed to provide further evidence to address whether treatment intensification by enzalutamide in the disease continuum (prior to the onset of metastasis or symptoms) is associated with improved metastasis-free survival (MFS) for men with high-risk nmCSPC with rising PSA after definitive therapy. Treatment with enzalutamide has shown robust effects across the prostate cancer continuum, including in patients with mCSPC (ARCHES[18] and ENZAMET[21]), patients with nmCRPC (PROSPER[22 23]), and patients with metastatic castration-resistant prostate cancer (PREVAIL[24–26] [chemotherapy naïve] and AFFIRM[27] [postchemotherapy]), supporting the expectation of a significant treatment effect in men with nmCSPC. This phase 3 randomised study will determine whether enzalutamide plus the LHRHa leuprolide or enzalutamide monotherapy is more effective than placebo plus leuprolide earlier in the prostate cancer continuum for patients with high-risk nmCSPC with PSA recurrence after local therapy.

We included a monotherapy arm based on the Tombal *et al* phase 2 study demonstrating rapid and durable PSA response described above.[15–17] EMBARK is therefore designed to provide additional evidence relating to the efficacy and safety of monotherapy as a rationale for avoiding adverse events associated with LHRHa therapy, including diabetes, ischemic heart disease, and osteoporosis,[28–30] but moreover to assess the QoL benefits of monotherapy.

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METHODS AND ANALYSIS

Study design

EMBARK is an international, randomised phase 3 study of enzalutamide plus LHRHa, enzalutamide monotherapy, and placebo plus LHRHa in men with high-risk nmCSPC with rising PSA after radical prostatectomy (RP), RT, or both (figure 1). High-risk patients with BCR after prior definitive therapy are characterized as having a PSADT ≤9 months and screening PSA of ≥1 ng/mL for patients who had prior RP (with or without RT) and ≥2 ng/mL above the nadir for patients who had primary RT only. These parameters were reached based on careful consideration of several factors, including the AUA definition of BCR (ie, detectable PSA level of ≥0.2 ng/mL, with a second confirmatory level >0.2 ng/mL after surgery)[31 32] along with the need for PSA to rise enough to calculate an accurate PSADT.[33] Considering the association of higher PSA with the onset of metastasis, a higher PSA cutoff would increase risk of metastases and need for ADT as standard of care prior to study eligibility. We therefore included patients with short duration of ADT (≤6 months given for rising PSA ≥9 months before the study to participate). This is also based on findings of median PSA at time of ADT post-RP treatment failure as shown to be 2.1 ng/mL in a multicentre Veteran's Administration cohort.[34]

Target enrollment was 1050 men with high-risk nmCSPC with rising PSA after RP, RT, or both. No prior cytotoxic chemotherapy or ADT treatment >6 months for BCR was allowed. The primary efficacy endpoint is MFS.

Inclusion and exclusion criteria

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The inclusion criteria are as follows (box 1): (1) patients aged ≥18 years; (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 RP, RT (including brachytherapy), or both, with curative intent; (4) PSADT ≤9 months; (5) screening PSA by the central laboratory ≥1 ng/mL for participants who had RP (with or without RT) as primary treatment for prostate cancer and ≥2 ng/mL above the nadir for participants who had RT only as primary treatment for prostate cancer; (6) serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening; and (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

Rationale for PSADT ≤9 months as a critical inclusion criterion: *Previous data in a cohort of men who had undergone RP and had subsequent BCR demonstrated PSADT (as well as time to BCR and Gleason score) was a significant factor predictive of the probability and time to development of metastatic disease.[7] To further stratify patients for risk of metastasis, a retrospective cohort of RP patients 16 years after BCR showed that PSADT (<3.0 versus 3.0–8.9 versus 9.0–14.9 versus ≥15.0 months), Gleason score (≤7 versus 8–10), and time from surgery to BCR (≤3 versus >3 years) were all significant risk factors for time to prostate-specific mortality.[8]*

The exclusion criteria are as follows: (1) prior or present evidence of distant metastatic disease as seen on computed tomography, magnetic resonance imaging, or bone scans; (2) prior hormonal therapy except for the following indications: neoadjuvant/adjuvant therapy to treat BCR ≤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; (3) for patients who had prior RP, a suitable candidate for salvage RT as determined by the investigator per guidelines (eg, ASTRO/AUA,[31] European Association of Urology[35]); (4) prior cytotoxic

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chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer; (5) prior systemic biologic therapy, including immunotherapy, for prostate cancer; (6) history of seizure or any condition that may predispose to seizure; and (7) clinically significant cardiovascular disease.

Dosage regimen

Randomization (1:1:1) assigned participants to one of the following study drug treatments: enzalutamide plus LHRHa (double-blind); placebo plus LHRHa (double-blind); or enzalutamide monotherapy (open-label). Enzalutamide is administered as 160 mg/day by mouth with or without food. Leuprolide 22.5 mg is given as a single intramuscular or subcutaneous injection every 12 weeks.

***Rationale**: A key feature of the protocol is having 1:1:1 randomization allowing for study of monotherapy versus ADT as a secondary endpoint. This is of special interest as an open-label single-arm phase 2 study of patients with nmCSPC and mCSPC treated with enzalutamide monotherapy demonstrated that this treatment led to a rapid and durable PSA response.*[15-17] *We are unaware of prior randomised controlled trials comparing next-generation oral antiandrogen monotherapy versus ADT in nmCSPC men with PSA-only recurrence. Current ASCO guidelines support consideration of CAB in this setting but with individualized benefit-risk assessment in consideration of its increased costs and potential for greater side effects.*

Study procedures

PSA is monitored throughout the study (at screening, weeks 1, 25, 36, 37, and 49, repeating every 3 months until criteria are met for permanent treatment discontinuation), and study drug treatment is suspended at week 37 for participants whose PSA values are undetectable (<0.2 ng/mL) at week 36 as determined by a central laboratory. Study drug treatment may be suspended only once (at week 37) due to undetectable PSA and reinitiated if subsequent PSA values increase to ≥2.0 ng/mL for participants with prior

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prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Participants with detectable PSA values (≥0.2 ng/mL) at week 36 continue treatment without suspension until permanent treatment discontinuation criteria are met.

***Rationale**: A key feature of the protocol is monitoring PSA levels at week 36 and suspending study drug treatment at week 37 for participants with undetectable PSA (<0.2 ng/mL), while continuing study treatment for those with detectable PSA. The rationale for this aspect of the design is data showing that IAD is noninferior to continuous ADT for overall survival in* nmCSPC*. IAD or an "IAD treatment holiday" in patients with* nmCSPC *may allow for clinical benefit along with modest improvements in QoL.*

Study endpoints

The primary endpoint is MFS between enzalutamide plus LHRHa and placebo plus LHRHa (table 1).

***Rationale**: To benefit men with early-stage disease and features indicating a high risk of morbidity and mortality from prostate cancer progression, a desirable therapy must demonstrate good efficacy in terms of delaying metastasis and death from prostate cancer, studied here using the defined primary endpoint of MFS, shown to be a surrogate of overall survival for patients with localized prostate cancer.*[36]

A key secondary endpoint is MFS between enzalutamide monotherapy versus placebo plus LHRHa.

***Rationale**: To assess the potential benefit of enzalutamide monotherapy compared with LHRHa based on phase 2 data showing rapid and durable PSA response with enzalutamide monotherapy.*[15–17]

Other key secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to PSA

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progression; (2) time to first use of antineoplastic therapy; and (3) overall survival. Other secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to distant metastasis; (2) proportion of participants per group who remain treatment-free 2 years after suspension of study drug at week 37 due to undetectable PSA; (3) proportion of participants per group with undetectable PSA 2 years after suspension of study drug at week 37 due to undetectable PSA; (4) proportion of participants per group with undetectable PSA at 36 weeks on study drug; (5) time to resumption of any hormonal therapy following suspension at week 37 due to undetectable PSA; (6) time to castration resistance; (7) time to symptomatic progression; (8) time to first symptomatic skeletal event; (9) time to clinically relevant pain (using the Brief Pain Inventory-Short Form [BPI-SF]); (10) quality of life, based on Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol 5-Dimension 5-Level Health Assessment Instrument (EQ-5D-5L), and EORTC Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25); and (11) safety.

Exploratory endpoints include progression-free survival after first subsequent therapy, defined as time from the date of randomisation to the first occurrence 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.

Efficacy assessments

Soft tissue disease is assessed by computed tomography or magnetic resonance imaging, with radiographic progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Bone disease is assessed by whole-body radionuclide

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bone scans, with radiographic progression defined as the appearance of one or more metastatic lesions on bone scan. Confirmation with a second imaging modality is required when bone lesions are found in a single region on the bone scan. Appearance of metastatic lesions in two or more of the five regions on a bone scan does not require confirmation with a second imaging modality.

Other efficacy assessments include survival status, serum PSA values, serum testosterone levels, resumption of any hormonal therapy, new antineoplastic therapy and surgery/interventions for prostate cancer, symptomatic skeletal events, and patient-reported outcomes (ie, BPI-SF, FACT-P, EQ-5D-5L, EORTC QLQ-PR25). The BPI-SF is a validated instrument using a self-reported scale assessing level of pain, its effects on activities of daily living, and analgesic medication use. The short form contains nine main pain-related questions rated on a scale of 0 to 10, with 10 being the worst pain.[37]

FACT-P is a self-reported multidimensional QoL instrument specifically designed for use in men with prostate cancer.[38] The questionnaire uses 27 core items to assess 4 domains of physical, social/family, emotional, and functional well-being and 12 site-specific items to assess prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain as well as a global QoL score, with higher scores representing better QoL.

EQ-5D-5L is a standardized instrument that measures health-related QoL.[39] Participants self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. They choose one of five possible responses that record level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. This tool also includes a visual analogue

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scale to self-rate general health state from “the worst health you can imagine” to “the best health you can imagine.”

EORTC QLQ-PR25 is a module of the EORTC QLQ-30 questionnaire developed to assess the QoL of patients with prostate cancer. Participants self-rate their current state of pain as it relates to urination, ease and frequency of urination, and bowel and other problems during the past week. Participants also answer five questions about weight loss/gain and sexual interest and four questions about sexual activity during the past 4 weeks. Participants choose one of four possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension.

Safety assessments include adverse events, clinical laboratory tests, physical examinations, and vital signs. An independent data monitoring committee will periodically monitor safety data.

Data analysis/statistical methods

The study requires approximately 1050 participants to achieve the targeted total number of events, assuming a 30-month improvement in median MFS in the enzalutamide plus LHRHa group compared with the placebo plus LHRHa group. The primary efficacy analysis of MFS is conducted using the intention-to-treat population, defined as all participants randomly assigned to study treatment. Efficacy analyses incorporates the stratification factors used at randomisation (screening PSA ≤10 ng/mL versus >10 ng/mL, PSADT ≤3 months versus >3 to ≤9 months, and prior hormonal versus no prior hormonal therapy). Treatment group comparisons are between the combination arms of enzalutamide plus LHRHa versus placebo plus LHRHa and between enzalutamide monotherapy versus placebo plus LHRHa. For the primary endpoint, MFS, the stratified

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log-rank test is used to compare enzalutamide plus LHRHa versus placebo plus LHRHa. Treatment effect is estimated by hazard ratios and 95% confidence intervals using a stratified Cox regression model. An interim analysis for efficacy/futility is planned.

Patient and public involvement

There was no patient or public involvement in the development of this manuscript, and none is planned at present.

Ethics and dissemination

The study is conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including Good Clinical Practice according to International Council for Harmonisation Guidelines. The results will be disseminated at several research conferences and as published articles in peer-reviewed journals.

Current trial status

The study completed enrollment on 14 June 2018.

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Contributors All authors have fulfilled authorship criteria.

SJF, UDeG, MG, BR,GPH, and NDS contributed to protocol design and manuscript preparation. QS and JS contributed to protocol design and the statistical analysis plan.

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Competing Interests SJF is a consultant to Astellas, Pfizer, Janssen, Bayer, Sanofi, Dendreon, Myovant, Astra Zeneca, and Merck. UDeG is a consultant to Astellas, Bayer, BMS, Ipsen, Janssen, Novartis, Pfizer, Sanofi, and Pharmamar; received institutional research funding from AstraZeneca, Roche, and Sanofi; and received travel funds from BMS, Ispen, Janssen, Pfizer, and Roche during the conduct of the study. MG has stock or ownership interest in OncoGenex Technologies, Sustained Therapeutics, and Sikta Pharmaceuticals; is a consultant to Astellas, AstraZeneca, Bayer, GDx, Janssen, Sanofi, Pfizer, Tersera and Roche; and holds patents for OGX-011, OGX-427, ST-CP and ST-POP. BR is an employee of and holds stock ownership in Pfizer. QS is an employee of Pfizer. JS is an employee of Astellas Pharma, Inc., with stock ownership in AstraZeneca. GPH is an employee of Astellas Pharma Global Development, Inc. NDS is a consultant to or received research funding from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Dendreon, Exact Sciences, Ferring, Fergene, Janssen, MDx Health, Merck, Myovant, Nymox, Pfizer, Sanofi and Tolmar.

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REFERENCES

1. Amling CL, Blute ML, Bergstralh EJ, *et al.* Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol* 2000;164101–5.
2. Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* 2005;66(suppl):83–94.
3. Chun FK, Graefen M, Zacharias M, *et al.* Anatomic radical retropubic prostatectomy-long-term recurrence-free survival rates for localized prostate cancer. *World J Urol* 2006;24:273–80.
4. Han M, Partin AW, Pound CR, *et al.* Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28:555–65.
5. Liesenfeld L, Kron M, Gschwend JE, *et al.* Prognostic factors for biochemical recurrence more than 10 years after radical prostatectomy. *J Urol* 2017;197:143-8.
6. Mottet N, Bellmunt J, Bolla M, *et al.* EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–29.
7. Pound CR, Partin AW, Eisenberger MA, *et al.* Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591–7.
8. Freedland SJ, Humphreys EB, Mangold LA, *et al.* Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433–9.
9. Freedland SJ, Humphreys EB, Mangold LA, *et al.* Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* 2007;25:1765–71.
10. Garcia-Albeniz X, Chan JM, Paciorek A, *et al.* Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse: an observational follow-up study. *Eur J Cancer* 2015;51(7):817–24.
11. Moul JW, Wu H, Sun L, *et al.* Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol* 2004;171:1141–7.
12. Lowrance W, Breau R, Chou R, *et al.* Advanced prostate cancer: AUA/ASTRO/SUO guideline. American Urological Association. Accessed August 20, 2020. http://www.auanet.org/guidelines/advanced-prostate-cancer.
13. Crook JM, O'Callaghan CJ, Duncan G, *et al.* Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367:895–903.
14. Loblaw DA, Virgo KS, Nam R, *et al.* Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25:1596–605.
15. Tombal B, Borre M, Rathenborg P, *et al.* Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol* 2014;15:592–600.

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16. Tombal B, Borre M, Rathenborg P, *et al.* Long-term efficacy and safety of enzalutamide monotherapy in hormone-naïve prostate cancer: 1- and 2-year open-label follow-up results. *Eur Urol* 2015;68:787–94.
17. Tombal B, Borre M, Rathenborg P, *et al.* Long-term antitumor activity and safety of enzalutamide monotherapy in hormone naïve prostate cancer: 3-year open label followup results. *J Urol* 2018;199:459–64.
18. Armstrong AJ, Szmulewitz RZ, Petrylak DP, *et al.* ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2019;37:2974–86.
19. Chi KN, Agarwal N, Bjartell A, *et al.* Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381:13–24.
20. Fizazi K, Tran N, Fein L, *et al.* Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–60.
21. Davis ID, Martin AJ, Stockler MR, *et al.* Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019;381(2):121–31.
22. Hussain M, Fizazi K, Saad F, *et al.* Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2018;378:2465–74.
23. Sternberg CN, Fizazi K, Saad F, *et al.* Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2020;382:2197–206.
24. Armstrong AJ, Lin P, Tombal B, *et al.* Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer from the PREVAIL trial. *Eur Urol* 2020;78:347–57.
25. Beer TM, Armstrong AJ, Rathkopf D, *et al.* Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. *Eur Urol* 2017;71:151–4.
26. Beer TM, Armstrong AJ, Rathkopf DE, *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:424–33.
27. Scher HI, Fizazi K, Saad F, *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–97.
28. Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. *Cancer* 2009;115:2388–99.
29. Keating NL, O'Malley AJ, Freedland SJ, *et al.* Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst* 2010;102:39–46.
30. Shahinian VB, Kuo YF, Freeman JL, *et al.* Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154–64.
31. Pisansky TM, Thompson IM, Valicenti RK, *et al.* Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline amendment 2018–2019. *J Urol* 2019;202:533–8.
32. Abramowitz MC, Li T, Buyyounouski MK, *et al.* The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer* 2008;112:55–60.
33. Arlen PM, Bianco F, Dahut WL, e*t al.* Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. *J Urol* 2008;179:2181–5.

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34. Keto CJ, Aronson WJ, Terris MK, *et al.* Detectable prostate-specific antigen Nadir during androgen-deprivation therapy predicts adverse prostate cancer-specific outcomes: results from the SEARCH database. *Eur Urol* 2014;65:620–7.
35. Cornford P, Bellmunt J, Bolla M, *et al.* EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol* 2017;71:630–42.
36. Xie W, Regan MM, Buyse M, *et al.* Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017;35:3097–104.
37. Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J Pain Symptom Manage* 1996;12:273–82.
38. Cella DF, Tulsky DS, Gray G, *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–9.
39. Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.

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Figures/Tables

Figure 1. EMBARK study design

Box 1. Eligibility criteria

Table 1. Objectives and endpoints

Supplementary Materials Infographic

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Figure Legend

Figure 1. EMBARK study design

*Study drug treatment reinitiated if PSA increases to ≥2.0 ng/mL for patients with prior prostatectomy or to ≥5.0 ng/mL for patients without prostatectomy.

†For enzalutamide plus LHRHa versus placebo plus LHRHa, and secondary endpoint for enzalutamide monotherapy versus placebo plus LHRHa.

LHRHa, luteinizing hormone-releasing hormone agonist; post-RP, post-radical prostatectomy; post-RT, post-radiation therapy; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; T, testosterone.

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Box 1. Eligibility criteria

Inclusion criteria

- Aged ≥18 years
- Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features
- Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent
- PSA doubling time ≤9 months
- 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 ≥2 ng/mL above the nadir for patients who had only radiotherapy as primary treatment for prostate cancer
- Serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening
- ECOG performance status of 0 or 1 at screening

Exclusion criteria

- Prior or present evidence of distant metastatic disease
- 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 is allowed
- For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator per guidelines (eg, American Society for Radiation Oncology/American Urological Association,[31] European Association of Urology[35])
- Prior cytotoxic chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer
- Prior systemic biologic therapy, including immunotherapy, for prostate cancer
- History of seizure or any condition that may predispose to seizure
- Clinically significant cardiovascular disease

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

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Table 1. Objectives and endpoints

Primary objective	**Primary endpoint**
• To evaluate the efficacy of enzalutamide plus LHRHa versus placebo plus LHRHa in patients with high-risk nmCSPC	• MFS between enzalutamide plus LHRHa versus LHRHa
Key secondary objectives	**Secondary endpoints**
• To evaluate efficacy of enzalutamide monotherapy versus placebo plus LHRHa	• MFS between enzalutamide monotherapy versus placebo plus LHRHa
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to PSA progression
	• Time to first use of antineoplastic therapy
	• Overall survival
Other secondary objectives	**Other secondary endpoints**
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to distant metastasis
	• Time to castration resistance
	• Time to symptomatic progression
	• Time to first symptomatic skeletal event (using the BPI-SF)
	• Time to clinically relevant pain
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa based on PSA at week 36 (ie, whereby treatment is suspended at week 37 in participants with undetectable levels of ≤0.2 ng/mL)	• Proportion of participants per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants 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
• To compare PROs in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• PROs as measured by FACT-P, EQ-5D-5L, and EORTC QLQ-PR25
• To compare overall safety in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• Safety (adverse events, clinical laboratory tests, physical examinations, and vital signs), monitored by independent data monitoring committee
Exploratory objective	**Exploratory endpoint**
• To compare progression-free survival after first subsequent therapy	• Time from the date of randomization to the first occurrence of investigator-determined disease progression

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BPI-SF, Brief Pain Inventory-Short Form; EORTC QLQ-PR25, EORTC Quality of Life Questionnaire-Prostate 25; EQ-5D-5L, EuroQol 5-Dimension 5-Level Health Assessment Instrument; FACT-P, Functional Assessment of Cancer Therapy-Prostate; LHRHa, luteinizing hormone–releasing hormone agonist; MFS, metastasis-free survival; nmCSPC, nonmetastatic castration-sensitive prostate cancer; PROs, patient-reported outcomes; PSA, prostate-specific antigen.

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Supplementary Materials Infographic

File submitted separately

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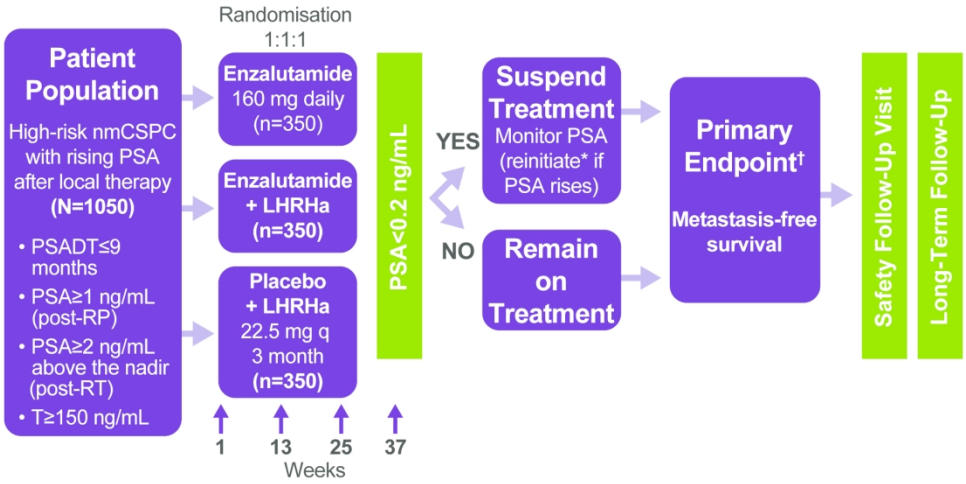

Figure 1

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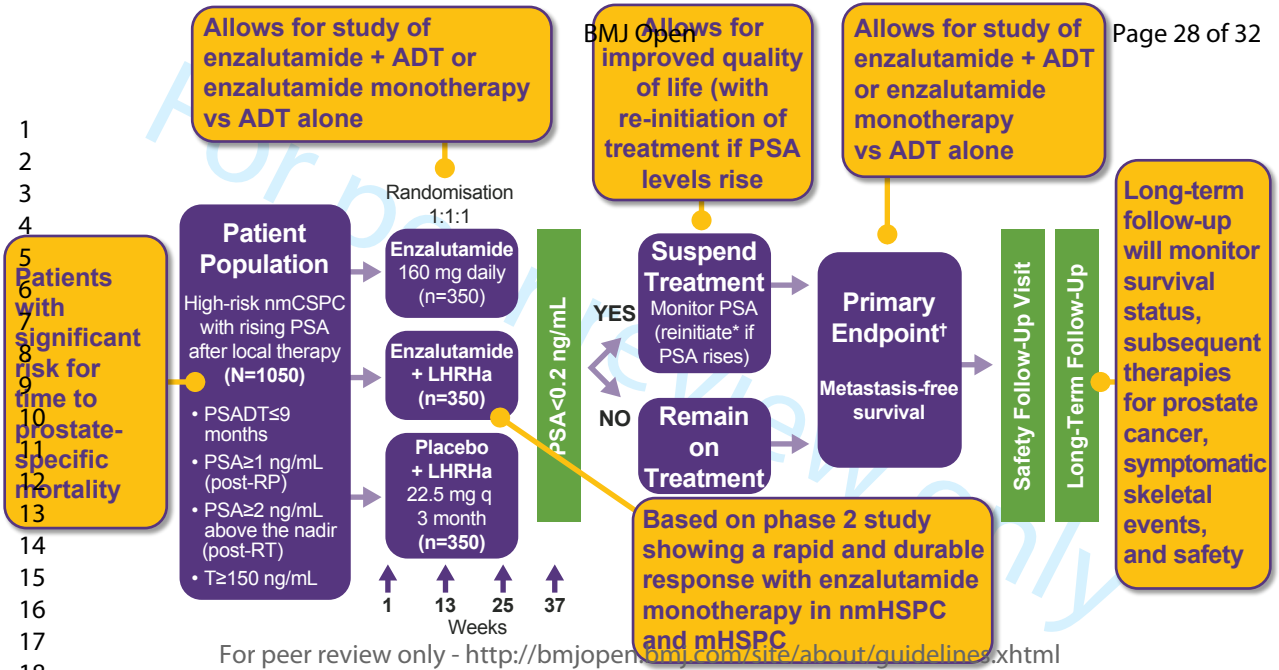

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EMBARK was designed to address whether treatment intensification by use of novel hormonal therapy early in the prostate cancer disease continuum (prior to the onset of metasta-sis/symptoms) is associated with improved metastasis-free survival

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	Not specified
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not specified

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____3-6_____
	6b	Explanation for choice of comparators	___ 3-6_____
Objectives	7	Specific objectives or hypotheses	___ 3-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Not specified___
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___7-8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____10_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____Not specified
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____Not specified
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____14_____

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____7_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____Not specified
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____Not specified
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____Not specified
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____Not specified
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____Not specified

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____Not specified
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____13-14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____N/A_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____Not specified
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____Not specified
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____Not specified
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____3_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____Not specified

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____Not specified
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____Not specified
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____Not specified
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ Not specified
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___Not specified
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____14_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__14-15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not specified___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_ Not included
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__Not specified

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology
Keywords:	Prostate disease < UROLOGY, Clinical trials < THERAPEUTICS, GENITOURINARY MEDICINE

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A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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Running head: EMBARK Study Design

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ABSTRACT (limit, 300 words): 299

Introduction Limited data from controlled clinical trials are available for men who experience biochemical recurrence after definitive therapy for prostate cancer. In the absence of overt metastases, patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) often receive androgen deprivation therapy (ADT). There is no standard-of-care consensus on optimal ADT timing, although most men are treated prior to metastases, especially those with high-risk features (Gleason score 8-10 or prostate-specific antigen doubling time [PSADT] <9–12 months). Given data that ADT plus novel hormonal agents improves survival in men with metastatic CSPC, there is a desire to evaluate these agents earlier in the disease course. The main objective of EMBARK is the comparative assessment of enzalutamide plus leuprolide (luteinizing hormone–releasing hormone agonist [LHRHa]) or enzalutamide monotherapy vs monotherapy LHRHa to improve metastasis-free survival (MFS) in patients with high-risk nmCSPC PSA recurrence after definitive therapy.

Methods and analysis EMBARK is a randomised, phase 3 study of high-risk patients with nmCSPC, a PSADT of ≤9 months, and a screening PSA of ≥2 ng/mL above the nadir after radiotherapy (RT) or ≥1 ng/mL after radical prostatectomy (RP) with or without postoperative RT. Men (N=1068) are randomised 1:1:1 to enzalutamide 160 mg/day plus LHRHa or placebo plus LHRHa (double-blind arms) or enzalutamide monotherapy (open-label arm). Treatment is suspended at Week 37 if PSA concentrations are <0.2 ng/mL and reinstated if levels rise to ≥2.0 ng/mL with RP or ≥5.0 ng/mL without RP. Patients with PSA ≥0.2 ng/mL at Week 37 continue until

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treatment discontinuation criteria are met. The primary endpoint is MFS comparing enzalutamide plus LHRHa versus placebo plus LHRHa.

Ethics and dissemination The study is conducted under the guiding principles of the World Medical Association Declaration of Helsinki. The results will be disseminated at research conferences and in peer-reviewed journals.

Trial registration number: NCT02319837

Strengths and limitations of this study

- EMBARK is the first study designed to determine whether early, combined therapy with enzalutamide plus a luteinizing hormone–releasing hormone agonist (LHRHa) or enzalutamide monotherapy is more effective than placebo plus LHRHa in patients with high-risk nonmetastatic castration resistant prostate cancer (nmCSPC).
- A PSA doubling time of ≤9 months is included as a critical inclusion criterion based on its prior demonstration as a significant risk factor for prostate cancer-specific mortality and the primary endpoint of MFS is a documented surrogate for OS in patients with localised disease.
- Monitoring PSA concentrations to inform treatment suspension in participants with undetectable PSA, and treatment continuation in those with detectable PSA, to evaluate whether intermittent ADT or an intermittent ADT holiday affords a clinical benefit together with modest improvements in quality of life, represents a principal feature of this protocol
- A limitation of this study is the absence of biomarker analysis for study of enzalutamide response and resistance mechanisms.
- An additional study limitation is that some patients may develop nonmetastatic castration-resistant prostate cancer before radiographic progression, based on prior PSA elevations, and discontinue their participation in the study

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INTRODUCTION

Background

Approximately one-third of patients experience biochemical recurrence (BCR; i.e., prostate-specific antigen [PSA]-only recurrence) within 10 years after primary definitive therapy for prostate cancer.[1-5] The rise in PSA concentration represents prostate cancer recurrence, as well as the likely presence of micrometastatic disease and an increased risk of prostate cancer–related morbidity and mortality.[6] Patients with PSA doubling time (PSADT) <9 months are at high risk for rapid progression to radiologically evident metastases and eventual death.[7-9]

Treatments are limited for patients with high-risk nonmetastatic castration-sensitive prostate cancer (nmCSPC) with evidence of disease recurrence by PSA but without overt metastases. Standard of care options include systemic treatment with androgen deprivation therapy (ADT; orchiectomy or luteinizing hormone–releasing hormone agonist [LHRHa] or LHRH antagonist), salvage local therapy, usually with radiotherapy (RT), or observation.[6] For these patients, there is no general clinical consensus on optimal ADT timing either with early treatment to delay progression and hopefully prolong survival or with later treatment once metastases and symptoms develop to lessen the risk of adverse effects.[10] Given limited data that early ADT may delay progression to metastases in high-risk patients exhibiting high-grade disease (eg., Gleason score of 8–10 or serum PSADT of <12 months),[11] this approach is commonly employed for high-risk men. For patients who have exhausted local treatment options, a recent guideline from the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and Society for Urologic Oncology recommends against

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routinely initiating ADT and using it as intermittent therapy if initiated. Guideline recommendations also call for observation or clinical trial enrollment.[12]

Rather than continuous ADT, another option is continuous versus intermittent androgen blockade (IAD), although the latter is considered noninferior to continuous ADT while offering modest quality-of-life (QoL) improvements in patients with nmCSPC.[13] Finally, there is no general consensus for the use of ADT alone versus ADT plus a first-generation, nonsteroidal antiandrogen [NSAA (bicalutamide, flutamide, and nilutamide)], known as combined androgen blockade (CAB), in patients with nmCSPC. American Society of Clinical Oncology (ASCO) guidelines suggest that CAB be considered in this setting, with personalized patient/physician treatment decisions in light of potential adverse effects and associated cost concerns.[14]

In an open-label, single-arm, phase 2 study of patients with nmCSPC and metastatic CSPC (mCSPC), treatment with enzalutamide monotherapy led to a rapid and durable response, with 92.5% of patients having a PSA decline of ≥80% at 25 weeks.[15] PSA response was maintained with a favorable tumor response and was well tolerated at subsequent 1-,[16] 2-,[16] and 3-year[17] open-label follow-ups. While promising, no phase 3 study has yet tested enzalutamide monotherapy. Given data that ADT and novel hormonal agents improve survival and/or radiographic progression–free survival in men with mCSPC, there is a desire to further evaluate such a combination even earlier in the disease course in a Phase 3 study.[18-20]

Rationale

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EMBARK is designed to provide further evidence to address whether treatment intensification by enzalutamide in the disease continuum (prior to the onset of metastasis or symptoms) is associated with improved metastasis-free survival (MFS) for men with high-risk nmCSPC and rising PSA concentrations after definitive therapy (figure 1). Treatment with enzalutamide has shown robust effects across the prostate cancer continuum, including in patients with mCSPC (ARCHES[18] and ENZAMET[21]), patients with nmCRPC (PROSPER[22 23]), and patients with metastatic castration-resistant prostate cancer (PREVAIL[24-26] [chemotherapy naïve] and AFFIRM[27] [post-chemotherapy]), supporting the expectation of a significant treatment effect in men with nmCSPC. This phase 3 randomised study will determine whether administration of enzalutamide plus LHRHa or enzalutamide monotherapy is more effective than placebo plus LHRHa earlier along the prostate cancer continuum for patients with high-risk nmCSPC and rising PSA levels after local therapy. The PSA values have been blinded from study investigators to ensure that metastatic events rather than periodic, serum PSA determinations guide in the clinical decision to change therapy.

We included a monotherapy arm based on the Tombal *et al* phase 2 study demonstrating a rapid and durable PSA response described above.[15-17] EMBARK is therefore designed to provide additional evidence relating to the efficacy and safety of monotherapy as a rationale for avoiding adverse events associated with LHRHa therapy, including diabetes, ischemic heart disease, and osteoporosis,[28-30] but moreover to assess the QoL benefits of monotherapy.

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METHODS AND ANALYSIS

Study design

EMBARK is an international, randomised phase 3 study of enzalutamide plus LHRHa, enzalutamide monotherapy, and placebo plus LHRHa in men with high-risk nmCSPC and rising PSA concentrations after radical prostatectomy (RP), RT, or both. The study was initiated on 17 December 2014 with target enrollment achieved on 18 June 2018. Study completion is estimated for 19 September 2026. High-risk patients with biochemical recurrence (BCR) after prior definitive therapy are characterized as having a PSADT ≤9 months and a screening PSA of ≥1 ng/mL for patients who underwent prior RP (with or without RT) and ≥2 ng/mL above the nadir for patients who received primary RT only. These parameters were reached based on careful consideration of several factors, including the AUA definition of BCR (i.e., detectable PSA level of ≥0.2 ng/mL, with a second confirmatory level >0.2 ng/mL after surgery)[31 32] along with the need for PSA to rise sufficiently to calculate an accurate PSADT.[33] Considering the association of elevated PSA levels with the onset of metastasis, a higher PSA cutoff would increase risk of metastases and need for ADT as standard of care prior to study eligibility. We therefore included patients with a short duration of ADT (≤6 months prescribed for a rising PSA ≥9 months prior to study entry). This decision also is based on findings of a median PSA level of 2.1 ng/mL at the time of ADT post-RP treatment failure in a multicentre Veteran's Administration cohort.[34]

Target enrollment was 1050 men with high-risk nmCSPC with rising PSA concentrations after RP, RT, or both. No prior cytotoxic chemotherapy or ADT treatment >6 months for BCR was allowed. The primary efficacy endpoint is MFS.

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Patient and public involvement

No patients were involved.

Inclusion and exclusion criteria

The inclusion criteria are as follows (box 1): (1) patients aged ≥18 years; (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 RP, RT (including brachytherapy), or both, with curative intent; (4) PSADT ≤9 months; (5) screening PSA by the central laboratory ≥1 ng/mL for participants who had RP (with or without RT) as primary treatment for prostate cancer and ≥2 ng/mL above the nadir for participants who had RT only as primary treatment for prostate cancer; (6) serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening; and (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

Rationale for PSADT ≤9 months as a critical inclusion criterion: *Previous data in a cohort of men who had undergone RP and developed subsequent BCR demonstrated that PSADT (as well as time to BCR and Gleason score) was a significant factor predictive of the probability and time to development of metastatic disease.[7] To further stratify patients for risk of metastasis, a retrospective cohort study of patients 16 years after post-prostatectomy BCR, reported that PSADT (<3.0 versus 3.0–8.9 versus 9.0–14.9 versus ≥15.0 months), Gleason score (≤7 versus 8–10), and time from surgery to BCR (≤3 versus >3 years) were all significant risk factors for time to prostate-specific mortality.[8]*

The exclusion criteria are as follows: (1) prior or present evidence of distant metastatic disease as seen on computed tomography, magnetic resonance imaging, or bone scans; (2) prior hormonal therapy except for the following indications:

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neoadjuvant/adjuvant therapy to treat BCR ≤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; (3) for patients who had prior RP, a suitable candidate for salvage RT as determined by the investigator per guidelines (e.g., ASTRO/AUA,[31] European Association of Urology[35]); (4) prior cytotoxic chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer; (5) prior systemic biologic therapy, including immunotherapy, for prostate cancer; (6) history of seizure or any condition that may predispose to seizure; and (7) clinically significant cardiovascular disease.

Dosage regimen

Central randomization (1:1:1) assigned study participants to one of the following treatment arms: enzalutamide plus LHRHa (double-blind); placebo plus LHRHa (double-blind); or enzalutamide monotherapy (open-label). Enzalutamide is administered as 160 mg/day by mouth with or without food. Leuprolide 22.5 mg is administered as a single intramuscular or subcutaneous injection every 12 weeks.

***Rationale**: A key feature of the protocol is having a 1:1:1 randomization that allows for the evaluation of monotherapy versus ADT as a secondary endpoint. This is of special interest as an open-label, single-arm, phase 2 study of patients with nmCSPC and mCSPC treated with enzalutamide monotherapy demonstrated that this treatment led to a rapid and durable PSA response.*[15-17] *We are unaware of prior randomised, controlled trials comparing next-generation, oral antiandrogen monotherapy versus ADT in men with nmCSPC and PSA-only recurrence. Current ASCO guidelines support consideration of CAB in this setting but with individualized benefit-risk assessment in consideration of its increased costs and potential for greater adverse effects.*

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Study procedures

A central laboratory will quantify on-treatment PSA concentrations. With the exception of screening PSA values, PSA results will not be provided to study site investigators or participants. Alternatively, study sites will be notified if any PSA level meets a specified concentration threshold and a PSADT ≤10 months while on study treatment. Imaging studies will be conducted every 6 months with computed tomography (CT) or magnetic resonance imaging (MRI) to detect soft tissue disease and whole-body radionuclide bone scintigraphy (RBS) for bony metastasis. Serum PSA concentrations are monitored throughout the study (at screening, weeks 1, 25, 36, 37, and 49, repeating every 3 months until criteria are met for permanent treatment discontinuation [i.e., signs of disease progression on conventional, radiographic imaging]), and study drug treatment is suspended at week 37 for participants whose PSA values are undetectable (<0.2 ng/mL) at week 36. Study drug treatment may be suspended only once (at week 37) due to undetectable PSA and reinitiated if subsequent PSA levels increase to ≥2.0 ng/mL for participants with prior prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Participants with detectable PSA concentrations (≥0.2 ng/mL) at week 36 continue treatment without suspension until permanent treatment discontinuation criteria are met.

***Rationale**: A key feature of the protocol is monitoring PSA levels at week 36 and suspending study drug treatment at week 37 for participants with undetectable PSA (<0.2 ng/mL), while continuing study treatment for those with detectable PSA. The rationale for this aspect of the design is data, which demonstrate that IAD is noninferior to continuous ADT for overall survival in nmCSPC. Intermittent androgen deprivation or an "IAD treatment holiday" in patients with* nmCSPC *may afford clinical benefit together with modest improvements in QoL.*

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Study endpoints

The primary endpoint is MFS between enzalutamide plus LHRHa and placebo plus LHRHa (table 1).

***Rationale**: To benefit men with early-stage disease and features that indicate a high risk of morbidity and mortality from prostate cancer progression, a desirable therapy must demonstrate good efficacy in terms of delaying metastasis and death from prostate cancer, studied here using the defined primary endpoint of MFS, shown to be a surrogate of OS for patients with localized prostate cancer.*[35]

A key secondary endpoint is MFS between enzalutamide monotherapy versus placebo plus LHRHa.

***Rationale**: To assess the potential clinical benefit of enzalutamide monotherapy compared with LHRHa based on phase 2 data showing a rapid and durable PSA response with enzalutamide monotherapy.*[15-17]

Other key secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to PSA progression; (2) time to first use of antineoplastic therapy; and (3) OS. Other secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to distant metastasis; (2) proportion of participants per group who remain treatment-free 2 years after suspension of study drug at week 37 due to undetectable PSA; (3) proportion of participants per group with undetectable PSA 2 years after suspension of study drug at week 37 due to undetectable PSA; (4) proportion of participants per group with undetectable PSA at 36 weeks on study drug; (5) time to resumption of any hormonal therapy following study drug suspension at week 37 due to undetectable PSA; (6) time to castration resistance;

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(7) time to symptomatic progression; (8) time to first symptomatic skeletal event (SSE); (9) time to clinically relevant pain (assessed with the Brief Pain Inventory-Short Form [BPI-SF]); (10) quality of life, based on Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol 5-Dimension 5-Level Health Assessment Instrument (EQ-5D-5L), and EORTC Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25); and (11) safety.

Exploratory endpoints include PFS after first subsequent therapy, defined as time from the date of randomisation to the first occurrence 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.

Efficacy and safety assessments

Soft tissue disease is assessed by CT or MRI, with radiographic progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Bony metastasis is assessed by whole-body RBS, with radiographic progression defined as the appearance of one or more metastatic lesions on bone scan. Confirmation with a second imaging modality is required when lesions are detected in a single region on the bone scan. Appearance of metastatic lesions in two or more of the five regions on a bone scan does not require confirmation with a second imaging modality.

Other efficacy assessments include survival status, serum PSA values, serum testosterone concentrations, resumption of any hormonal therapy, new antineoplastic therapy, surgery/interventions for prostate cancer, SSEs, and patient-reported outcomes (ie, BPI-SF, FACT-P, EQ-5D-5L, EORTC QLQ-PR25). The BPI-SF is a

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validated instrument using a self-reported scale to assess level of pain, its effects on activities of daily living, and analgesic use. The short form contains nine, main, pain-related items rated on a severity and interference with activity scale of 0 to 10, with 10 representing the worst pain.[36]

FACT-P is a self-reported, multidimensional QoL instrument specifically designed for use in men with prostate cancer.[37] The questionnaire uses 27 core items to assess 4 domains of physical, social/family, emotional, and functional well-being and 12 site-specific items to assess prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain as well as a global QoL score, with higher scores representing better QoL.

EQ-5D-5L is a standardized instrument that measures health-related QoL.[38] Participants self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. They choose one of five possible responses that record level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. This tool also includes a visual analogue scale to describe general state of health from “the worst health you can imagine” to “the best health you can imagine.”

EORTC QLQ-PR25 is a module of the EORTC QLQ-30 questionnaire developed to assess the QoL of patients with prostate cancer. Participants self-rate their current state of pain as it relates to urination, ease and frequency of urination, and bowel and other discomforts during the past week. Participants also answer five questions on weight loss/gain and sexual interest and four questions about sexual activity during the past 4

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weeks. Participants choose one of four possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension.

Safety assessments include adverse events, clinical laboratory tests, physical examinations, and vital signs.

Periodic monitoring of safety data as well as evaluation of interim efficacy results from this study will be conducted by an independent, external, Data Monitoring Committee of experts in prostate cancer, safety data monitoring, and statistics.

Data analysis/statistical methods

Statistical assumptions (MFS hazard ratio, 0.75) in the original EMBARK protocol were considered to be too conservative based on clinical trial results from SPARTAN[39] and PROSPER[22]. Therefore, the number of patients required for enrollment was reduced from 1860 to 1050 when the statistical plan was amended in June 2018. The study requires approximately 1050 participants to achieve the targeted total number of events, assuming a 30-month improvement in median MFS in the enzalutamide plus LHRHa group compared with the placebo plus LHRHa group. The primary efficacy analysis of MFS is conducted using the intention-to-treat (ITT) population, defined as all participants randomly assigned to study treatment. Efficacy analyses incorporates the stratification factors applied at randomisation (screening PSA ≤10 ng/mL versus >10 ng/mL, PSADT ≤3 months versus >3 to ≤9 months, and prior hormonal therapy versus no prior hormonal therapy). Treatment group comparisons are between the combination arms of enzalutamide plus LHRHa versus placebo plus LHRHa and between enzalutamide monotherapy versus placebo plus LHRHa. For the primary endpoint, MFS, the stratified log-rank test is employed to compare enzalutamide plus LHRHa

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versus placebo plus LHRHa. Treatment effect is estimated by hazard ratios and 95% confidence intervals using a stratified Cox regression model. An interim analysis for efficacy/futility is planned.

Ethics and dissemination

The study is conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including Good Clinical Practice according to International Council for Harmonisation Guidelines. Ethics committee approval will be obtained for extensive protocol amendments. All patients were required by study investigator to provide informed consent prior to start of the study (Supplementary file 1). Patient identify information will remain confidential as specified in the protocol or longer if required by local regulations. The results will be disseminated at several research conferences and as published articles in peer-reviewed journals after approval from the study sponsors.

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Contributors All authors have fulfilled authorship criteria.

SJF, UDeG, MG, BR,GPH, and NDS contributed to protocol design and manuscript preparation. QS and JS contributed to protocol design and the statistical analysis plan.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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REFERENCES

1. Amling CL, Blute ML, Bergstralh EJ, et al. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol* 2000;164(1):101-5. [published Online First: 2000/06/07]
2. Bianco FJ, Jr., Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* 2005;66(5 Suppl):83-94. doi: 10.1016/j.urology.2005.06.116 [published Online First: 2005/10/01]
3. Chun FK, Graefen M, Zacharias M, et al. Anatomic radical retropubic prostatectomy-long-term recurrence-free survival rates for localized prostate cancer. *World J Urol* 2006;24(3):273-80. doi: 10.1007/s00345-006-0058-2 [published Online First: 2006/03/01]
4. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28(3):555-65. doi: 10.1016/s0094-0143(05)70163-4 [published Online First: 2001/10/10]
5. Liesenfeld L, Kron M, Gschwend JE, et al. Prognostic Factors for Biochemical Recurrence More than 10 Years after Radical Prostatectomy. *J Urol* 2017;197(1):143-48. doi: 10.1016/j.juro.2016.07.004 [published Online First: 2016/07/16]
6. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017;71(4):618-29. doi: 10.1016/j.eururo.2016.08.003 [published Online First: 2016/08/30]
7. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-7. doi: 10.1001/jama.281.17.1591 [published Online First: 1999/05/11]
8. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294(4):433-9. doi: 10.1001/jama.294.4.433 [published Online First: 2005/07/28]
9. Freedland SJ, Humphreys EB, Mangold LA, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* 2007;25(13):1765-71. doi: 10.1200/JCO.2006.08.0572 [published Online First: 2007/05/02]
10. Garcia-Albeniz X, Chan JM, Paciorek A, et al. Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study. *Eur J Cancer* 2015;51(7):817-24. doi: 10.1016/j.ejca.2015.03.003 [published Online First: 2015/03/22]
11. Moul JW, Wu H, Sun L, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol* 2004;171(3):1141-7. doi: 10.1097/01.ju.0000113794.34810.d0 [published Online First: 2004/02/10]
12. Association AU. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline 2020 [Available from: http://www.auanet.org/guidelines/advanced-prostate-cancer accessed August 20, 2020.
13. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367(10):895-903. doi: 10.1056/NEJMoa1201546 [published Online First: 2012/08/31]
14. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25(12):1596-605. doi: 10.1200/JCO.2006.10.1949 [published Online First: 2007/04/04]

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15. Tombal B, Borre M, Rathenborg P, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol* 2014;15(6):592-600. doi: 10.1016/S1470-2045(14)70129-9 [published Online First: 2014/04/18]
16. Tombal B, Borre M, Rathenborg P, et al. Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naive Prostate Cancer: 1- and 2-Year Open-label Follow-up Results. *Eur Urol* 2015;68(5):787-94. doi: 10.1016/j.eururo.2015.01.027 [published Online First: 2015/02/18]
17. Tombal B, Borre M, Rathenborg P, et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naive Prostate Cancer: 3-Year Open Label Followup Results. *J Urol* 2018;199(2):459-64. doi: 10.1016/j.juro.2017.08.103 [published Online First: 2017/09/05]
18. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol* 2019;37(32):2974-86. doi: 10.1200/JCO.19.00799 [published Online First: 2019/07/23]
19. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307 [published Online First: 2019/06/01]
20. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017;377(4):352-60. doi: 10.1056/NEJMoa1704174 [published Online First: 2017/06/06]
21. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med* 2019;381(2):121-31. doi: 10.1056/NEJMoa1903835 [published Online First: 2019/06/04]
22. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2018;378(26):2465-74. doi: 10.1056/NEJMoa1800536 [published Online First: 2018/06/28]
23. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2020;382(23):2197-206. doi: 10.1056/NEJMoa2003892 [published Online First: 2020/05/30]
24. Armstrong AJ, Lin P, Tombal B, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol* 2020 doi: 10.1016/j.eururo.2020.04.061 [published Online First: 2020/06/13]
25. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol* 2017;71(2):151-54. doi: 10.1016/j.eururo.2016.07.032 [published Online First: 2016/08/02]
26. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371(5):424-33. doi: 10.1056/NEJMoa1405095 [published Online First: 2014/06/03]
27. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-97. doi: 10.1056/NEJMoa1207506 [published Online First: 2012/08/17]
28. Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. *Cancer* 2009;115(11):2388-99. doi: 10.1002/cncr.24283 [published Online First: 2009/04/29]
29. Keating NL, O'Malley AJ, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J*

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Natl Cancer Inst 2010;102(1):39-46. doi: 10.1093/jnci/djp404 [published Online First: 2009/12/10]
30. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352(2):154-64. doi: 10.1056/NEJMoa041943 [published Online First: 2005/01/14]
31. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline Amendment 2018-2019. *J Urol* 2019;202(3):533-38. doi: 10.1097/ju.0000000000000295 [published Online First: 2019/05/02]
32. Abramowitz MC, Li T, Buyyounouski MK, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer* 2008;112(1):55-60. doi: 10.1002/cncr.23139 [published Online First: 2007/10/31]
33. Arlen PM, Bianco F, Dahut WL, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. *J Urol* 2008;179(6):2181-5; discussion 85-6. doi: 10.1016/j.juro.2008.01.099 [published Online First: 2008/04/22]
34. Keto CJ, Aronson WJ, Terris MK, et al. Detectable prostate-specific antigen Nadir during androgen-deprivation therapy predicts adverse prostate cancer-specific outcomes: results from the SEARCH database. *Eur Urol* 2014;65(3):620-7. doi: 10.1016/j.eururo.2012.11.052 [published Online First: 2012/12/19]
35. Xie W, Regan MM, Buyse M, et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol* 2017;35(27):3097-104. doi: 10.1200/JCO.2017.73.9987 [published Online First: 2017/08/11]
36. Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J Pain Symptom Manage* 1996;12(5):273-82. doi: 10.1016/s0885-3924(96)00149-2 [published Online First: 1996/11/01]
37. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-9. doi: 10.1200/JCO.1993.11.3.570 [published Online First: 1993/03/01]
38. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 2011/04/12]
39. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med* 2018;378(15):1408-18. doi: 10.1056/NEJMoa1715546 [published Online First: 2018/02/09]
40. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol* 2017;71(4):630-42. doi: 10.1016/j.eururo.2016.08.002 [published Online First: 2016/09/07]

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Figures/Tables

Figure 1. EMBARK study design

Box 1. Eligibility criteria

Table 1. Objectives and endpoints

Supplementary file 1_Patient consent form

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Figure Legend

Figure 1. EMBARK study design

*Study drug treatment reinitiated if PSA increases to ≥2.0 ng/mL for patients with prior prostatectomy or to ≥5.0 ng/mL for patients without prostatectomy.

†For enzalutamide plus LHRHa versus placebo plus LHRHa, and secondary endpoint for enzalutamide monotherapy versus placebo plus LHRHa.

ADT, androgen deprivation therapy; LHRHa, luteinizing hormone-releasing hormone agonist; mHSPC, metastatic hormone-sensitive prostate cancer; nmCSPC, nonmetastatic castration-sensitive prostate cancer; nmHSPC, nonmetastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PSADT, PSA doubling time; T, testosterone.

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Box 1. Eligibility criteria

Inclusion criteria

- Aged ≥18 years
- Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features
- Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent
- PSA doubling time ≤9 months
- 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 ≥2 ng/mL above the nadir for patients who had only radiotherapy as primary treatment for prostate cancer
- Serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening
- ECOG performance status of 0 or 1 at screening

Exclusion criteria

- Prior or present evidence of distant metastatic disease
- 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 is allowed
- For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator per guidelines (eg, American Society for Radiation Oncology/American Urological Association,[31] European Association of Urology[31 40])
- Prior cytotoxic chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer
- Prior systemic biologic therapy, including immunotherapy, for prostate cancer
- History of seizure or any condition that may predispose to seizure
- Clinically significant cardiovascular disease

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

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Table 1. Objectives and endpoints

Primary objective	**Primary endpoint**
• To evaluate the efficacy of enzalutamide plus LHRHa versus placebo plus LHRHa in patients with high-risk nmCSPC	• MFS between enzalutamide plus LHRHa versus LHRHa
Key secondary objectives	**Secondary endpoints**
• To evaluate efficacy of enzalutamide monotherapy versus placebo plus LHRHa	• MFS between enzalutamide monotherapy versus placebo plus LHRHa
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to PSA progression
	• Time to first use of antineoplastic therapy
	• Overall survival
Other secondary objectives	**Other secondary endpoints**
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to distant metastasis
	• Time to castration resistance
	• Time to symptomatic progression
	• Time to first symptomatic skeletal event (using the BPI-SF)
	• Time to clinically relevant pain
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa based on PSA at week 36 (ie, whereby treatment is suspended at week 37 in participants with undetectable levels of ≤0.2 ng/mL)	• Proportion of participants per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants 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
• To compare PROs in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• PROs as measured by FACT-P, EQ-5D-5L, and EORTC QLQ-PR25
• To compare overall safety in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• Safety (adverse events, clinical laboratory tests, physical examinations, and vital signs), monitored by independent data monitoring committee
Exploratory objective	**Exploratory endpoint**
• To compare progression-free survival after first subsequent therapy	• Time from the date of randomization to the first occurrence of investigator-determined disease progression

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BPI-SF, Brief Pain Inventory-Short Form; EORTC QLQ-PR25, EORTC Quality of Life Questionnaire-Prostate 25; EQ-5D-5L, EuroQol 5-Dimension 5-Level Health Assessment Instrument; FACT-P, Functional Assessment of Cancer Therapy-Prostate; LHRHa, luteinizing hormone–releasing hormone agonist; MFS, metastasis-free survival; nmCSPC, nonmetastatic castration-sensitive prostate cancer; PROs, patient-reported outcomes; PSA, prostate-specific antigen

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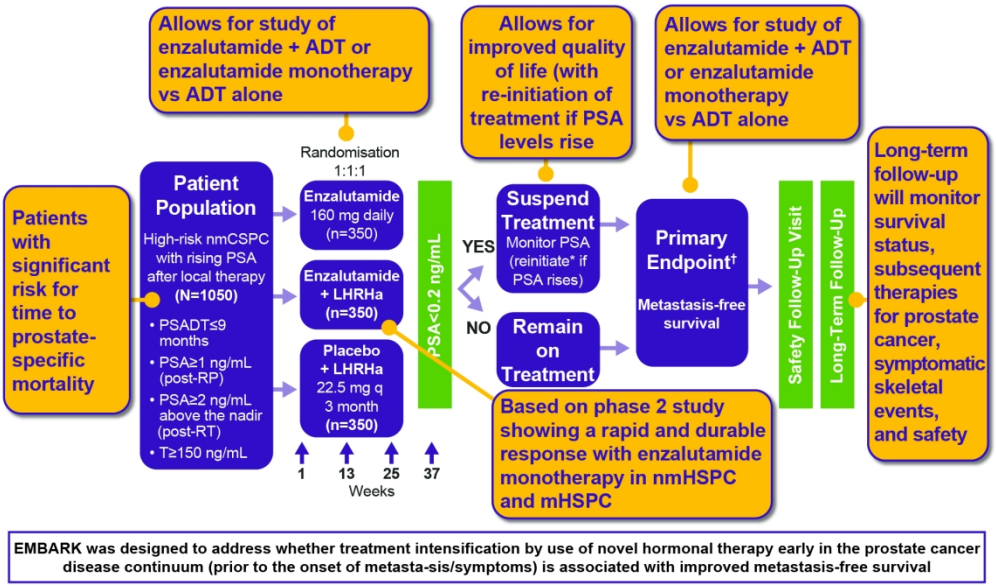

Figure 1

170x100mm (300 x 300 DPI)

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Supplementary file 1_Patient consent form

Consent to Take Part in the EMBARK Study

This is an abbreviated version of the full patient consent form provided to the trial participants.

Agreement to Participate and to Process Data	Participant Initials
1. I confirm I have read (or, if I cannot read, a study team member has read to me) and understand this consent document for the study described above and have had the opportunity to ask questions. I have had enough time to review this consent document. I also have had an opportunity to ask about the details of the study and to decide whether or not to participate.	
2. I have read and understand the Privacy Supplement. I understand that taking part in the study will require the processing (including collection, use, transfer, storage, analysis and reporting) of my personal information, as explained in the Privacy Supplement. I understand and agree to the processing of my personal information within and outside my country of residence for health care, medical research and/or regulatory purposes.	
3. I understand that taking part is voluntary and that I am free to stop taking part in this study or to withdraw my consent to the processing of my personal information at any time. I do not need to give any reason and my regular medical care and legal rights will not be affected. However, even if I withdraw my consent to processing, my personal information held at that time may be kept to comply with laws and regulations and to maintain the integrity of the study. I also understand that my biological samples may not be able to be destroyed because they may no longer be traceable to me, may have already been used, or may have been given to a third party.	
4. I agree to the study team accessing my medical history, including information from medical records and test results and any medical treatment I receive during the course of the study, and if necessary, contacting my doctor or any other health care providers treating me for access to such information.	
5. I understand that the Sponsor and/or others working with or on behalf of the Sponsor, institutional review boards (IRBs) or independent ethics committees (IECs), and regulatory agencies may need access to personal information about me generated at the study site or collected by the study team for the study and any	

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other research. I agree that they may have access to my personal information.	
6. I do not give up any of my legal rights by signing this consent document. I have been told that I will receive a signed and dated copy of this document.	
7. I agree to take part in the study described in this document.	

_____

Printed name of participant

_____

Signature of participant Date of signature[§]
(If no legally acceptable representative is used)

_____

Printed name of legally acceptable representative Relationship
(if applicable)

_____

Signature of legally acceptable representative Date of signature[§]
(if applicable)

Person Obtaining Consent:

_____

Printed Name of the Person Conducting the Consent Discussion

_____

Signature of the Person Conducting the Consent Discussion [†] Date of signature

[†]The investigator, or an appropriately qualified and trained person designated by the investigator to conduct the informed consent process, must sign and date the consent document during the same discussion when the participant signs the consent document.

Consent for Participant Who Cannot Read:
The study participant has indicated that he/she is unable to read. One or more members of the study team read the consent document to the study participant, discussed it with the study participant, and gave the study participant an opportunity to ask questions.

_____

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Printed name of impartial witness ‡

_____ _____

Signature of impartial witness Date of signature§

☐ Not applicable (*Check this box if the Signature of an impartial witness is not required. Signature of an impartial witness is required if the participant or the participant's legally acceptable representative cannot read.*)

§Participant/legally acceptable representative/impartial witness must personally date their signature.

‡ Impartial Witness: A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the participant. *See* Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	Not specified
Funding	4	Sources and types of financial, material, and other support	16–17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	16–17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16–17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not specified

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-7
	6b	Explanation for choice of comparators	3-7
Objectives	7	Specific objectives or hypotheses	3-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8, figure 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Not specified
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9–10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10–11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not specified
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not specified
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11–13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10–11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15–16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not specified
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not specified
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10–11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not specified
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11

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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____Not specified
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____Not specified
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____13–15_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____N/A_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____Not specified
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____15_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____Not specified
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____3_____

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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ 16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___Not specified
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__16–17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not specified___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supp file 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A

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BMJ Open

A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk nonmetastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

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Running head: EMBARK Study Design

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ABSTRACT (limit, 300 words): 299

Introduction Limited data from controlled clinical trials are available for men who experience biochemical recurrence after definitive therapy for prostate cancer. In the absence of overt metastases, patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) often receive androgen deprivation therapy (ADT). There is no standard-of-care consensus on optimal ADT timing, although most men are treated prior to metastases, especially those with high-risk features (Gleason score 8-10 or prostate-specific antigen doubling time [PSADT] <9–12 months). Given data that ADT plus novel hormonal agents improves survival in men with metastatic CSPC, there is a desire to evaluate these agents earlier in the disease course. The main objective of EMBARK is the comparative assessment of enzalutamide plus leuprolide (luteinizing hormone–releasing hormone agonist [LHRHa]) or enzalutamide monotherapy vs monotherapy LHRHa to improve metastasis-free survival (MFS) in patients with high-risk nmCSPC PSA recurrence after definitive therapy.

Methods and analysis EMBARK is a randomised, phase 3 study of high-risk patients with nmCSPC, a PSADT of ≤9 months, and a screening PSA of ≥2 ng/mL above the nadir after radiotherapy (RT) or ≥1 ng/mL after radical prostatectomy (RP) with or without postoperative RT. Men (N=1050) are randomised 1:1:1 to enzalutamide 160 mg/day plus LHRHa or placebo plus LHRHa (double-blind arms) or enzalutamide monotherapy (open-label arm). Treatment is suspended at Week 37 if PSA concentrations are <0.2 ng/mL and reinstated if levels rise to ≥2.0 ng/mL with RP or ≥5.0 ng/mL without RP. Patients with PSA ≥0.2 ng/mL at Week 37 continue until

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treatment discontinuation criteria are met. The primary endpoint is MFS comparing enzalutamide plus LHRHa versus placebo plus LHRHa.

Ethics and dissemination The study is conducted under the guiding principles of the World Medical Association Declaration of Helsinki. The results will be disseminated at research conferences and in peer-reviewed journals.

Trial registration number: NCT02319837

Strengths and limitations of this study

- EMBARK is the first study designed to determine whether early, combined therapy with enzalutamide plus a luteinizing hormone–releasing hormone agonist (LHRHa) or enzalutamide monotherapy is more effective than placebo plus LHRHa in patients with high-risk nonmetastatic castration resistant prostate cancer (nmCSPC).
- A PSA doubling time of ≤9 months is included as a critical inclusion criterion based on its prior demonstration as a significant risk factor for prostate cancer-specific mortality and the primary endpoint of MFS is a documented surrogate for OS in patients with localised disease.
- Monitoring PSA concentrations to inform treatment suspension in participants with undetectable PSA, and treatment continuation in those with detectable PSA, to evaluate whether intermittent ADT or an intermittent ADT holiday affords a clinical benefit together with modest improvements in quality of life, represents a principal feature of this protocol
- A limitation of this study is the absence of biomarker analysis for study of enzalutamide response and resistance mechanisms.
- An additional study limitation is that some patients may develop nonmetastatic castration-resistant prostate cancer before radiographic progression, based on prior PSA elevations, and discontinue their participation in the study

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INTRODUCTION

Background

Approximately one-third of patients experience biochemical recurrence (BCR; i.e., prostate-specific antigen [PSA]-only recurrence) within 10 years after primary definitive therapy for prostate cancer.[1-5] The rise in PSA concentration represents prostate cancer recurrence, as well as the likely presence of micrometastatic disease and an increased risk of prostate cancer–related morbidity and mortality.[6] Patients with PSA doubling time (PSADT) <9 months are at high risk for rapid progression to radiologically evident metastases and eventual death.[7-9]

Treatments are limited for patients with high-risk nonmetastatic castration-sensitive prostate cancer (nmCSPC) with evidence of disease recurrence by PSA but without overt metastases. Standard of care options include systemic treatment with androgen deprivation therapy (ADT; orchiectomy or luteinizing hormone–releasing hormone agonist [LHRHa] or LHRH antagonist), salvage local therapy, usually with radiotherapy (RT), or observation.[6] For these patients, there is no general clinical consensus on optimal ADT timing either with early treatment to delay progression and hopefully prolong survival or with later treatment once metastases and symptoms develop to lessen the risk of adverse effects.[10] Given limited data that early ADT may delay progression to metastases in high-risk patients exhibiting high-grade disease (eg., Gleason score of 8–10 or serum PSADT of <12 months),[11] this approach is commonly employed for high-risk men. For patients who have exhausted local treatment options, a recent guideline from the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and Society for Urologic Oncology recommends against

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routinely initiating ADT and using it as intermittent therapy if initiated. Guideline recommendations also call for observation or clinical trial enrollment.[12]

Rather than continuous ADT, another option is continuous versus intermittent androgen blockade (IAD), although the latter is considered noninferior to continuous ADT while offering modest quality-of-life (QoL) improvements in patients with nmCSPC.[13] Finally, there is no general consensus for the use of ADT alone versus ADT plus a first-generation, nonsteroidal antiandrogen [NSAA (bicalutamide, flutamide, and nilutamide)], known as combined androgen blockade (CAB), in patients with nmCSPC. American Society of Clinical Oncology (ASCO) guidelines suggest that CAB be considered in this setting, with personalized patient/physician treatment decisions in light of potential adverse effects and associated cost concerns.[14]

In an open-label, single-arm, phase 2 study of patients with nmCSPC and metastatic CSPC (mCSPC), treatment with enzalutamide monotherapy led to a rapid and durable response, with 92.5% of patients having a PSA decline of ≥80% at 25 weeks.[15] PSA response was maintained with a favorable tumor response and was well tolerated at subsequent 1-,[16] 2-,[16] and 3-year[17] open-label follow-ups. While promising, no phase 3 study has yet tested enzalutamide monotherapy. Given data that ADT and novel hormonal agents improve survival and/or radiographic progression–free survival in men with mCSPC, there is a desire to further evaluate such a combination even earlier in the disease course in a Phase 3 study.[18-20]

Rationale

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EMBARK is designed to provide further evidence to address whether treatment intensification by enzalutamide in the disease continuum (prior to the onset of metastasis or symptoms) is associated with improved metastasis-free survival (MFS) for men with high-risk nmCSPC and rising PSA concentrations after definitive therapy (figure 1). Treatment with enzalutamide has shown robust effects across the prostate cancer continuum, including in patients with mCSPC (ARCHES[18] and ENZAMET[21]), patients with nmCRPC (PROSPER[22 23]), and patients with metastatic castration-resistant prostate cancer (PREVAIL[24-26] [chemotherapy naïve] and AFFIRM[27] [post-chemotherapy]), supporting the expectation of a significant treatment effect in men with nmCSPC. This phase 3 randomised study will determine whether administration of enzalutamide plus LHRHa or enzalutamide monotherapy is more effective than placebo plus LHRHa earlier along the prostate cancer continuum for patients with high-risk nmCSPC and rising PSA levels after local therapy. The PSA values have been blinded from study investigators to ensure that metastatic events rather than periodic, serum PSA determinations guide in the clinical decision to change therapy.

We included a monotherapy arm based on the Tombal *et al* phase 2 study demonstrating a rapid and durable PSA response described above.[15-17] EMBARK is therefore designed to provide additional evidence relating to the efficacy and safety of monotherapy as a rationale for avoiding adverse events associated with LHRHa therapy, including diabetes, ischemic heart disease, and osteoporosis,[28-30] but moreover to assess the QoL benefits of monotherapy.

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METHODS AND ANALYSIS

Study design

EMBARK is an international, randomised phase 3 study of enzalutamide plus LHRHa, enzalutamide monotherapy, and placebo plus LHRHa in men with high-risk nmCSPC and rising PSA concentrations after radical prostatectomy (RP), RT, or both. The study was initiated on 17 December 2014 with target enrollment achieved on 18 June 2018. Study completion is estimated for 19 September 2026. High-risk patients with biochemical recurrence (BCR) after prior definitive therapy are characterized as having a PSADT ≤9 months and a screening PSA of ≥1 ng/mL for patients who underwent prior RP (with or without RT) and ≥2 ng/mL above the nadir for patients who received primary RT only. These parameters were reached based on careful consideration of several factors, including the AUA definition of BCR (i.e., detectable PSA level of ≥0.2 ng/mL, with a second confirmatory level >0.2 ng/mL after surgery)[31 32] along with the need for PSA to rise sufficiently to calculate an accurate PSADT.[33] Considering the association of elevated PSA levels with the onset of metastasis, a higher PSA cutoff would increase risk of metastases and need for ADT as standard of care prior to study eligibility. We therefore included patients with a short duration of ADT (≤6 months prescribed for a rising PSA ≥9 months prior to study entry). This decision also is based on findings of a median PSA level of 2.1 ng/mL at the time of ADT post-RP treatment failure in a multicentre Veteran's Administration cohort.[34]

Target enrollment was 1050 men with high-risk nmCSPC with rising PSA concentrations after RP, RT, or both. No prior cytotoxic chemotherapy or ADT treatment >6 months for BCR was allowed. The primary efficacy endpoint is MFS.

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Patient and public involvement

No patients were involved.

Inclusion and exclusion criteria

The inclusion criteria are as follows (box 1): (1) patients aged ≥18 years; (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 RP, RT (including brachytherapy), or both, with curative intent; (4) PSADT ≤9 months; (5) screening PSA by the central laboratory ≥1 ng/mL for participants who had RP (with or without RT) as primary treatment for prostate cancer and ≥2 ng/mL above the nadir for participants who had RT only as primary treatment for prostate cancer; (6) serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening; and (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at screening.

Rationale for PSADT ≤9 months as a critical inclusion criterion: *Previous data in a cohort of men who had undergone RP and developed subsequent BCR demonstrated that PSADT (as well as time to BCR and Gleason score) was a significant factor predictive of the probability and time to development of metastatic disease.[7] To further stratify patients for risk of metastasis, a retrospective cohort study of patients 16 years after post-prostatectomy BCR, reported that PSADT (<3.0 versus 3.0–8.9 versus 9.0–14.9 versus ≥15.0 months), Gleason score (≤7 versus 8–10), and time from surgery to BCR (≤3 versus >3 years) were all significant risk factors for time to prostate-specific mortality.[8]*

The exclusion criteria are as follows: (1) prior or present evidence of distant metastatic disease as seen on computed tomography, magnetic resonance imaging, or bone scans; (2) prior hormonal therapy except for the following indications:

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neoadjuvant/adjuvant therapy to treat BCR ≤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; (3) for patients who had prior RP, a suitable candidate for salvage RT as determined by the investigator per guidelines (e.g., ASTRO/AUA,[31] European Association of Urology[35]); (4) prior cytotoxic chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer; (5) prior systemic biologic therapy, including immunotherapy, for prostate cancer; (6) history of seizure or any condition that may predispose to seizure; and (7) clinically significant cardiovascular disease.

Dosage regimen

Central randomization (1:1:1) assigned study participants to one of the following treatment arms: enzalutamide plus LHRHa (double-blind); placebo plus LHRHa (double-blind); or enzalutamide monotherapy (open-label). Enzalutamide is administered as 160 mg/day by mouth with or without food. Leuprolide 22.5 mg is administered as a single intramuscular or subcutaneous injection every 12 weeks.

***Rationale**: A key feature of the protocol is having a 1:1:1 randomization that allows for the evaluation of monotherapy versus ADT as a secondary endpoint. This is of special interest as an open-label, single-arm, phase 2 study of patients with nmCSPC and mCSPC treated with enzalutamide monotherapy demonstrated that this treatment led to a rapid and durable PSA response.*[15-17] *We are unaware of prior randomised, controlled trials comparing next-generation, oral antiandrogen monotherapy versus ADT in men with nmCSPC and PSA-only recurrence. Current ASCO guidelines support consideration of CAB in this setting but with individualized benefit-risk assessment in consideration of its increased costs and potential for greater adverse effects.*

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Study procedures

A central laboratory will quantify on-treatment PSA concentrations. With the exception of screening PSA values, PSA results will not be provided to study site investigators or participants. Alternatively, study sites will be notified if any PSA level meets a specified concentration threshold and a PSADT ≤10 months while on study treatment. Imaging studies will be conducted every 6 months with computed tomography (CT) or magnetic resonance imaging (MRI) to detect soft tissue disease and whole-body radionuclide bone scintigraphy (RBS) for bony metastasis. Serum PSA concentrations are monitored throughout the study (at screening, weeks 1, 25, 36, 37, and 49, repeating every 3 months until criteria are met for permanent treatment discontinuation [i.e., signs of disease progression on conventional, radiographic imaging]), and study drug treatment is suspended at week 37 for participants whose PSA values are undetectable (<0.2 ng/mL) at week 36. Study drug treatment may be suspended only once (at week 37) due to undetectable PSA and reinitiated if subsequent PSA levels increase to ≥2.0 ng/mL for participants with prior prostatectomy or ≥5.0 ng/mL for patients without prostatectomy. Participants with detectable PSA concentrations (≥0.2 ng/mL) at week 36 continue treatment without suspension until permanent treatment discontinuation criteria are met.

***Rationale**: A key feature of the protocol is monitoring PSA levels at week 36 and suspending study drug treatment at week 37 for participants with undetectable PSA (<0.2 ng/mL), while continuing study treatment for those with detectable PSA. The rationale for this aspect of the design is data, which demonstrate that IAD is noninferior to continuous ADT for overall survival in nmCSPC. Intermittent androgen deprivation or an "IAD treatment holiday" in patients with* nmCSPC *may afford clinical benefit together with modest improvements in QoL.*

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Study endpoints

The primary endpoint is MFS between enzalutamide plus LHRHa and placebo plus LHRHa (table 1).

***Rationale**: To benefit men with early-stage disease and features that indicate a high risk of morbidity and mortality from prostate cancer progression, a desirable therapy must demonstrate good efficacy in terms of delaying metastasis and death from prostate cancer, studied here using the defined primary endpoint of MFS, shown to be a surrogate of OS for patients with localized prostate cancer.*[35]

A key secondary endpoint is MFS between enzalutamide monotherapy versus placebo plus LHRHa.

***Rationale**: To assess the potential clinical benefit of enzalutamide monotherapy compared with LHRHa based on phase 2 data showing a rapid and durable PSA response with enzalutamide monotherapy.*[15-17]

Other key secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to PSA progression; (2) time to first use of antineoplastic therapy; and (3) OS. Other secondary endpoints of enzalutamide plus LHRHa combination therapy or enzalutamide monotherapy versus placebo plus LHRHa are: (1) time to distant metastasis; (2) proportion of participants per group who remain treatment-free 2 years after suspension of study drug at week 37 due to undetectable PSA; (3) proportion of participants per group with undetectable PSA 2 years after suspension of study drug at week 37 due to undetectable PSA; (4) proportion of participants per group with undetectable PSA at 36 weeks on study drug; (5) time to resumption of any hormonal therapy following study drug suspension at week 37 due to undetectable PSA; (6) time to castration resistance;

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(7) time to symptomatic progression; (8) time to first symptomatic skeletal event (SSE); (9) time to clinically relevant pain (assessed with the Brief Pain Inventory-Short Form [BPI-SF]); (10) quality of life, based on Functional Assessment of Cancer Therapy-Prostate (FACT-P), EuroQol 5-Dimension 5-Level Health Assessment Instrument (EQ-5D-5L), and EORTC Quality of Life Questionnaire-Prostate 25 (EORTC QLQ-PR25); and (11) safety.

Exploratory endpoints include PFS after first subsequent therapy, defined as time from the date of randomisation to the first occurrence 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.

Efficacy and safety assessments

Soft tissue disease is assessed by CT or MRI, with radiographic progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Bony metastasis is assessed by whole-body RBS, with radiographic progression defined as the appearance of one or more metastatic lesions on bone scan. Confirmation with a second imaging modality is required when lesions are detected in a single region on the bone scan. Appearance of metastatic lesions in two or more of the five regions on a bone scan does not require confirmation with a second imaging modality.

Other efficacy assessments include survival status, serum PSA values, serum testosterone concentrations, resumption of any hormonal therapy, new antineoplastic therapy, surgery/interventions for prostate cancer, SSEs, and patient-reported outcomes (ie, BPI-SF, FACT-P, EQ-5D-5L, EORTC QLQ-PR25). The BPI-SF is a

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validated instrument using a self-reported scale to assess level of pain, its effects on activities of daily living, and analgesic use. The short form contains nine, main, pain-related items rated on a severity and interference with activity scale of 0 to 10, with 10 representing the worst pain.[36]

FACT-P is a self-reported, multidimensional QoL instrument specifically designed for use in men with prostate cancer.[37] The questionnaire uses 27 core items to assess 4 domains of physical, social/family, emotional, and functional well-being and 12 site-specific items to assess prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale and then combined to produce subscale scores for each domain as well as a global QoL score, with higher scores representing better QoL.

EQ-5D-5L is a standardized instrument that measures health-related QoL.[38] Participants self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. They choose one of five possible responses that record level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. This tool also includes a visual analogue scale to describe general state of health from “the worst health you can imagine” to “the best health you can imagine.”

EORTC QLQ-PR25 is a module of the EORTC QLQ-30 questionnaire developed to assess the QoL of patients with prostate cancer. Participants self-rate their current state of pain as it relates to urination, ease and frequency of urination, and bowel and other discomforts during the past week. Participants also answer five questions on weight loss/gain and sexual interest and four questions about sexual activity during the past 4

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weeks. Participants choose one of four possible responses that record level of intensity (not at all, a little, quite a bit, very much) within each dimension.

Safety assessments include adverse events, clinical laboratory tests, physical examinations, and vital signs.

Periodic monitoring of safety data as well as evaluation of interim efficacy results from this study will be conducted by an independent, external, Data Monitoring Committee of experts in prostate cancer, safety data monitoring, and statistics.

Data analysis/statistical methods

Statistical assumptions (MFS hazard ratio, 0.75) in the original EMBARK protocol were considered to be too conservative based on clinical trial results from SPARTAN[39] and PROSPER[22]. Therefore, the number of patients required for enrollment was reduced from 1860 to 1050 when the statistical plan was amended in June 2018. The study requires approximately 1050 participants to achieve the targeted total number of events, assuming a 30-month improvement in median MFS in the enzalutamide plus LHRHa group compared with the placebo plus LHRHa group. The primary efficacy analysis of MFS is conducted using the intention-to-treat (ITT) population, defined as all participants randomly assigned to study treatment. Efficacy analyses incorporates the stratification factors applied at randomisation (screening PSA ≤10 ng/mL versus >10 ng/mL, PSADT ≤3 months versus >3 to ≤9 months, and prior hormonal therapy versus no prior hormonal therapy). Treatment group comparisons are between the combination arms of enzalutamide plus LHRHa versus placebo plus LHRHa and between enzalutamide monotherapy versus placebo plus LHRHa. For the primary endpoint, MFS, the stratified log-rank test is employed to compare enzalutamide plus LHRHa

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versus placebo plus LHRHa. Treatment effect is estimated by hazard ratios and 95% confidence intervals using a stratified Cox regression model. An interim analysis for efficacy/futility is planned.

Ethics and dissemination

The study is conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including Good Clinical Practice according to International Council for Harmonisation Guidelines. Ethics committee approval will be obtained for extensive protocol amendments. All patients were required by study investigator to provide informed consent prior to start of the study (Supplementary file 1). Patient identify information will remain confidential as specified in the protocol or longer if required by local regulations. The results will be disseminated at several research conferences and as published articles in peer-reviewed journals after approval from the study sponsors.

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Contributors All authors have fulfilled authorship criteria.

SJF, UDeG, MG, BR,GPH, and NDS contributed to protocol design and manuscript preparation. QS and JS contributed to protocol design and the statistical analysis plan.

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Competing Interests SJF is a consultant to Astellas, Pfizer, Janssen, Bayer, Sanofi, Dendreon, Myovant, Astra Zeneca, and Merck. UDeG is a consultant to Astellas, Bayer, BMS, Ipsen, Janssen, Novartis, Pfizer, Sanofi, and Pharmamar; received institutional research funding from AstraZeneca, Roche, and Sanofi; and received travel funds from BMS, Ispen, Janssen, Pfizer, and Roche during the conduct of the study. MG has stock or ownership interest in OncoGenex Technologies, Sustained Therapeutics, and Sikta Pharmaceuticals; is a consultant to Astellas, AstraZeneca, Bayer, GDx, Janssen, Sanofi, Pfizer, Tersera and Roche; and holds patents for OGX-011, OGX-427, ST-CP and ST-POP. BR is an employee of and holds stock ownership in Pfizer. QS is an employee of Pfizer. JS is an employee of Astellas Pharma, Inc., with stock ownership in AstraZeneca. GPH is an employee of Astellas Pharma Global Development, Inc. NDS is a consultant to or received research funding from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, BMS, Dendreon, Exact Sciences, Ferring, Fergene, Janssen, MDx Health, Merck, Myovant, Nymox, Pfizer, Sanofi and Tolmar.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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REFERENCES

1. Amling CL, Blute ML, Bergstralh EJ, et al. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol* 2000;164(1):101-5. [published Online First: 2000/06/07]
2. Bianco FJ, Jr., Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* 2005;66(5 Suppl):83-94. doi: 10.1016/j.urology.2005.06.116 [published Online First: 2005/10/01]
3. Chun FK, Graefen M, Zacharias M, et al. Anatomic radical retropubic prostatectomy-long-term recurrence-free survival rates for localized prostate cancer. *World J Urol* 2006;24(3):273-80. doi: 10.1007/s00345-006-0058-2 [published Online First: 2006/03/01]
4. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28(3):555-65. doi: 10.1016/s0094-0143(05)70163-4 [published Online First: 2001/10/10]
5. Liesenfeld L, Kron M, Gschwend JE, et al. Prognostic Factors for Biochemical Recurrence More than 10 Years after Radical Prostatectomy. *J Urol* 2017;197(1):143-48. doi: 10.1016/j.juro.2016.07.004 [published Online First: 2016/07/16]
6. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017;71(4):618-29. doi: 10.1016/j.eururo.2016.08.003 [published Online First: 2016/08/30]
7. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-7. doi: 10.1001/jama.281.17.1591 [published Online First: 1999/05/11]
8. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294(4):433-9. doi: 10.1001/jama.294.4.433 [published Online First: 2005/07/28]
9. Freedland SJ, Humphreys EB, Mangold LA, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol* 2007;25(13):1765-71. doi: 10.1200/JCO.2006.08.0572 [published Online First: 2007/05/02]
10. Garcia-Albeniz X, Chan JM, Paciorek A, et al. Immediate versus deferred initiation of androgen deprivation therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study. *Eur J Cancer* 2015;51(7):817-24. doi: 10.1016/j.ejca.2015.03.003 [published Online First: 2015/03/22]
11. Moul JW, Wu H, Sun L, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol* 2004;171(3):1141-7. doi: 10.1097/01.ju.0000113794.34810.d0 [published Online First: 2004/02/10]
12. Association AU. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline 2020 [Available from: http://www.auanet.org/guidelines/advanced-prostate-cancer accessed August 20, 2020.
13. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. *N Engl J Med* 2012;367(10):895-903. doi: 10.1056/NEJMoa1201546 [published Online First: 2012/08/31]
14. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25(12):1596-605. doi: 10.1200/JCO.2006.10.1949 [published Online First: 2007/04/04]

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15. Tombal B, Borre M, Rathenborg P, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol* 2014;15(6):592-600. doi: 10.1016/S1470-2045(14)70129-9 [published Online First: 2014/04/18]
16. Tombal B, Borre M, Rathenborg P, et al. Long-term Efficacy and Safety of Enzalutamide Monotherapy in Hormone-naive Prostate Cancer: 1- and 2-Year Open-label Follow-up Results. *Eur Urol* 2015;68(5):787-94. doi: 10.1016/j.eururo.2015.01.027 [published Online First: 2015/02/18]
17. Tombal B, Borre M, Rathenborg P, et al. Long-Term Antitumor Activity and Safety of Enzalutamide Monotherapy in Hormone Naive Prostate Cancer: 3-Year Open Label Followup Results. *J Urol* 2018;199(2):459-64. doi: 10.1016/j.juro.2017.08.103 [published Online First: 2017/09/05]
18. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol* 2019;37(32):2974-86. doi: 10.1200/JCO.19.00799 [published Online First: 2019/07/23]
19. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2019;381(1):13-24. doi: 10.1056/NEJMoa1903307 [published Online First: 2019/06/01]
20. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017;377(4):352-60. doi: 10.1056/NEJMoa1704174 [published Online First: 2017/06/06]
21. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med* 2019;381(2):121-31. doi: 10.1056/NEJMoa1903835 [published Online First: 2019/06/04]
22. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2018;378(26):2465-74. doi: 10.1056/NEJMoa1800536 [published Online First: 2018/06/28]
23. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med* 2020;382(23):2197-206. doi: 10.1056/NEJMoa2003892 [published Online First: 2020/05/30]
24. Armstrong AJ, Lin P, Tombal B, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. *Eur Urol* 2020 doi: 10.1016/j.eururo.2020.04.061 [published Online First: 2020/06/13]
25. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol* 2017;71(2):151-54. doi: 10.1016/j.eururo.2016.07.032 [published Online First: 2016/08/02]
26. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371(5):424-33. doi: 10.1056/NEJMoa1405095 [published Online First: 2014/06/03]
27. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-97. doi: 10.1056/NEJMoa1207506 [published Online First: 2012/08/17]
28. Taylor LG, Canfield SE, Du XL. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. *Cancer* 2009;115(11):2388-99. doi: 10.1002/cncr.24283 [published Online First: 2009/04/29]
29. Keating NL, O'Malley AJ, Freedland SJ, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J*

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Natl Cancer Inst 2010;102(1):39-46. doi: 10.1093/jnci/djp404 [published Online First: 2009/12/10]
30. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352(2):154-64. doi: 10.1056/NEJMoa041943 [published Online First: 2005/01/14]
31. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and Salvage Radiotherapy after Prostatectomy: ASTRO/AUA Guideline Amendment 2018-2019. *J Urol* 2019;202(3):533-38. doi: 10.1097/ju.0000000000000295 [published Online First: 2019/05/02]
32. Abramowitz MC, Li T, Buyyounouski MK, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer* 2008;112(1):55-60. doi: 10.1002/cncr.23139 [published Online First: 2007/10/31]
33. Arlen PM, Bianco F, Dahut WL, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. *J Urol* 2008;179(6):2181-5; discussion 85-6. doi: 10.1016/j.juro.2008.01.099 [published Online First: 2008/04/22]
34. Keto CJ, Aronson WJ, Terris MK, et al. Detectable prostate-specific antigen Nadir during androgen-deprivation therapy predicts adverse prostate cancer-specific outcomes: results from the SEARCH database. *Eur Urol* 2014;65(3):620-7. doi: 10.1016/j.eururo.2012.11.052 [published Online First: 2012/12/19]
35. Xie W, Regan MM, Buyse M, et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol* 2017;35(27):3097-104. doi: 10.1200/JCO.2017.73.9987 [published Online First: 2017/08/11]
36. Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J Pain Symptom Manage* 1996;12(5):273-82. doi: 10.1016/s0885-3924(96)00149-2 [published Online First: 1996/11/01]
37. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-9. doi: 10.1200/JCO.1993.11.3.570 [published Online First: 1993/03/01]
38. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First: 2011/04/12]
39. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med* 2018;378(15):1408-18. doi: 10.1056/NEJMoa1715546 [published Online First: 2018/02/09]
40. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol* 2017;71(4):630-42. doi: 10.1016/j.eururo.2016.08.002 [published Online First: 2016/09/07]

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Figures/Tables

Figure 1. EMBARK study design

Box 1. Eligibility criteria

Table 1. Objectives and endpoints

Supplementary file 1_Patient consent form

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Figure Legend

Figure 1. EMBARK study design

*Study drug treatment reinitiated if PSA increases to ≥2.0 ng/mL for patients with prior prostatectomy or to ≥5.0 ng/mL for patients without prostatectomy.

†For enzalutamide plus LHRHa versus placebo plus LHRHa, and secondary endpoint for enzalutamide monotherapy versus placebo plus LHRHa.

ADT, androgen deprivation therapy; LHRHa, luteinizing hormone-releasing hormone agonist; mHSPC, metastatic hormone-sensitive prostate cancer; nmCSPC, nonmetastatic castration-sensitive prostate cancer; nmHSPC, nonmetastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen; PSADT, PSA doubling time; T, testosterone.

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Box 1. Eligibility criteria

Inclusion criteria

- Aged ≥18 years
- Histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet cell, or small cell features
- Prostate cancer initially treated by radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent
- PSA doubling time ≤9 months
- 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 ≥2 ng/mL above the nadir for patients who had only radiotherapy as primary treatment for prostate cancer
- Serum testosterone ≥150 ng/dL (5.2 nmol/L) at screening
- ECOG performance status of 0 or 1 at screening

Exclusion criteria

- Prior or present evidence of distant metastatic disease
- 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 is allowed
- For patients who had a prior prostatectomy, a suitable candidate for salvage radiotherapy as determined by the investigator per guidelines (eg, American Society for Radiation Oncology/American Urological Association,[31] European Association of Urology[31 40])
- Prior cytotoxic chemotherapy, abiraterone acetate, or enzalutamide for prostate cancer
- Prior systemic biologic therapy, including immunotherapy, for prostate cancer
- History of seizure or any condition that may predispose to seizure
- Clinically significant cardiovascular disease

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

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Table 1. Objectives and endpoints

Primary objective	**Primary endpoint**
• To evaluate the efficacy of enzalutamide plus LHRHa versus placebo plus LHRHa in patients with high-risk nmCSPC	• MFS between enzalutamide plus LHRHa versus LHRHa
Key secondary objectives	**Secondary endpoints**
• To evaluate efficacy of enzalutamide monotherapy versus placebo plus LHRHa	• MFS between enzalutamide monotherapy versus placebo plus LHRHa
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to PSA progression
	• Time to first use of antineoplastic therapy
	• Overall survival
Other secondary objectives	**Other secondary endpoints**
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa in improving other efficacy measures	• Time to distant metastasis
	• Time to castration resistance
	• Time to symptomatic progression
	• Time to first symptomatic skeletal event (using the BPI-SF)
	• Time to clinically relevant pain
• To compare enzalutamide plus LHRHa and enzalutamide alone versus placebo plus LHRHa based on PSA at week 36 (ie, whereby treatment is suspended at week 37 in participants with undetectable levels of ≤0.2 ng/mL)	• Proportion of participants per group who remain treatment-free 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants per group with undetectable PSA 2 years after suspension of study drug treatment at week 37 due to undetectable PSA
	• Proportion of participants 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
• To compare PROs in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• PROs as measured by FACT-P, EQ-5D-5L, and EORTC QLQ-PR25
• To compare overall safety in enzalutamide plus LHRHa and enzalutamide alone arms versus placebo plus LHRHa arm	• Safety (adverse events, clinical laboratory tests, physical examinations, and vital signs), monitored by independent data monitoring committee
Exploratory objective	**Exploratory endpoint**
• To compare progression-free survival after first subsequent therapy	• Time from the date of randomization to the first occurrence of investigator-determined disease progression

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BPI-SF, Brief Pain Inventory-Short Form; EORTC QLQ-PR25, EORTC Quality of Life Questionnaire-Prostate 25; EQ-5D-5L, EuroQol 5-Dimension 5-Level Health Assessment Instrument; FACT-P, Functional Assessment of Cancer Therapy-Prostate; LHRHa, luteinizing hormone–releasing hormone agonist; MFS, metastasis-free survival; nmCSPC, nonmetastatic castration-sensitive prostate cancer; PROs, patient-reported outcomes; PSA, prostate-specific antigen

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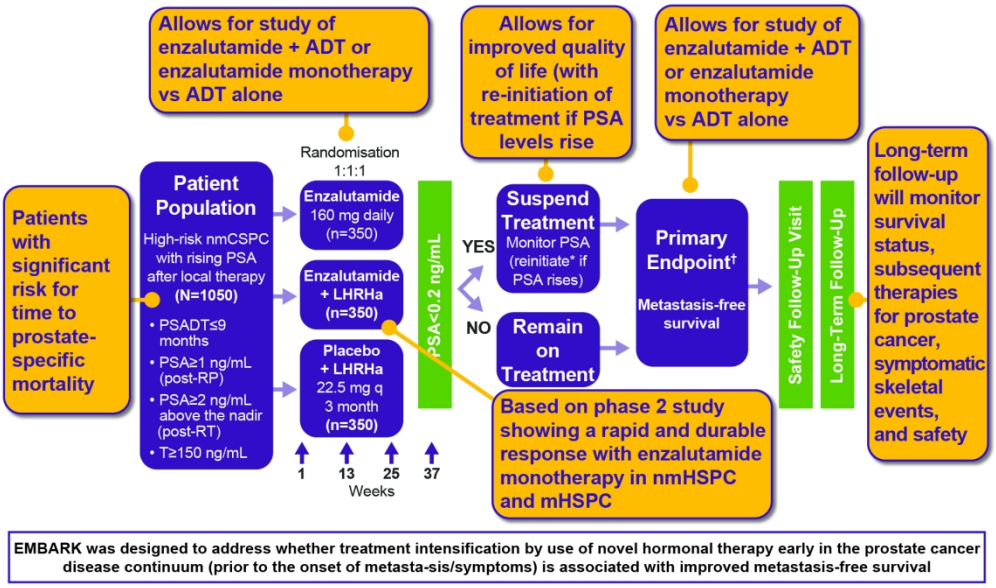

Figure 1

170x100mm (300 x 300 DPI)

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Supplementary file 1_Patient consent form

Consent to Take Part in the EMBARK Study

This is an abbreviated version of the full patient consent form provided to the trial participants.

Agreement to Participate and to Process Data	Participant Initials
1. I confirm I have read (or, if I cannot read, a study team member has read to me) and understand this consent document for the study described above and have had the opportunity to ask questions. I have had enough time to review this consent document. I also have had an opportunity to ask about the details of the study and to decide whether or not to participate.	
2. I have read and understand the Privacy Supplement. I understand that taking part in the study will require the processing (including collection, use, transfer, storage, analysis and reporting) of my personal information, as explained in the Privacy Supplement. I understand and agree to the processing of my personal information within and outside my country of residence for health care, medical research and/or regulatory purposes.	
3. I understand that taking part is voluntary and that I am free to stop taking part in this study or to withdraw my consent to the processing of my personal information at any time. I do not need to give any reason and my regular medical care and legal rights will not be affected. However, even if I withdraw my consent to processing, my personal information held at that time may be kept to comply with laws and regulations and to maintain the integrity of the study. I also understand that my biological samples may not be able to be destroyed because they may no longer be traceable to me, may have already been used, or may have been given to a third party.	
4. I agree to the study team accessing my medical history, including information from medical records and test results and any medical treatment I receive during the course of the study, and if necessary, contacting my doctor or any other health care providers treating me for access to such information.	
5. I understand that the Sponsor and/or others working with or on behalf of the Sponsor, institutional review boards (IRBs) or independent ethics committees (IECs), and regulatory agencies may need access to personal information about me generated at the study site or collected by the study team for the study and any	

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other research. I agree that they may have access to my personal information.	
6. I do not give up any of my legal rights by signing this consent document. I have been told that I will receive a signed and dated copy of this document.	
7. I agree to take part in the study described in this document.	

_____

Printed name of participant

_____

Signature of participant Date of signature[§]
(If no legally acceptable representative is used)

_____

Printed name of legally acceptable representative Relationship
(if applicable)

_____

Signature of legally acceptable representative Date of signature[§]
(if applicable)

Person Obtaining Consent:

_____

Printed Name of the Person Conducting the Consent Discussion

_____

Signature of the Person Conducting the Consent Discussion [†] Date of signature

[†]The investigator, or an appropriately qualified and trained person designated by the investigator to conduct the informed consent process, must sign and date the consent document during the same discussion when the participant signs the consent document.

Consent for Participant Who Cannot Read:
The study participant has indicated that he/she is unable to read. One or more members of the study team read the consent document to the study participant, discussed it with the study participant, and gave the study participant an opportunity to ask questions.

_____

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Printed name of impartial witness ‡

_____ _____

Signature of impartial witness Date of signature§

☐ Not applicable (*Check this box if the Signature of an impartial witness is not required. Signature of an impartial witness is required if the participant or the participant's legally acceptable representative cannot read.*)

§Participant/legally acceptable representative/impartial witness must personally date their signature.

‡ Impartial Witness: A person, who is independent of the study, who cannot be unfairly influenced by people involved with the study, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the participant. *See* Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	Not specified
Funding	4	Sources and types of financial, material, and other support	16–17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	16–17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16–17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not specified

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-7
	6b	Explanation for choice of comparators	3-7
Objectives	7	Specific objectives or hypotheses	3-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8, figure 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Not specified
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9–10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10–11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not specified
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not specified
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11–13

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10–11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15–16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not specified
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not specified
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10–11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not specified
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11

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	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____Not specified
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____Not specified
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____13–15_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____N/A_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____Not specified
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____15_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____Not specified
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____3_____

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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___ 16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___Not specified
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__16–17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not specified___
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Supp file 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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