Supplementary Material

Appendix 1

Key exclusion criteria included severe concurrent diseases, comorbidities or infections, known or suspected brain metastases, history of seizures, history of another malignancy within the past 5 years, clinically significant cardiovascular disease, or gastrointestinal disorder affecting absorption. Patients were also excluded for major surgery, the use of opiate analgesics for pain, or treatment with systemic biologic therapy, flutamide, ketoconazole, 5α-reductase inhibitors, estrogens, cyproterone, or an investigational agent within 4 weeks, radiation therapy (primary tumor) within 3 weeks, or bicalutamide or nilutamide within 6 weeks before the Day 1 visit.
### Table S1 Definition of disease progression at study entry and study endpoints

| Disease progression at study entry* | Definition                                                                 |
|------------------------------------|---------------------------------------------------------------------------|
| PSA progression†                  | Minimum of two rising PSA levels with an interval of at least 1 week between measurements and a minimum PSA of 2 µg/L or greater at screening |
| Soft-tissue disease progression   | RECIST, version 1.1, by CT/MRI                                             |
| Bone disease progression          | PCWG2 with two or more new lesions on bone scan                            |

### Study endpoints

| Primary                          | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| TTPP                             | Time from randomization to PSA progression†                               |
|                                  | For patients with a PSA decline at week 13, the PSA progression date was defined as the date when an increase of at least 25% and an absolute increase of at least 2 ng/mL above the nadir was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later |
|                                  | For patients without a PSA decline at Week 13, the PSA progression date was defined as the date when an increase of at least 25% and an absolute increase of at least 2 ng/mL above baseline was documented, which was confirmed by a second consecutive value obtained 3 or more weeks later |

| Secondary                        | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| OS                               | Time from randomization to death from any cause                           |
| rPFS                             | Time from randomization to an rPFS event confirmed by central independent radiology review, or death from any cause within 168 days of treatment discontinuation, whichever occurred first |
| Time to first SRE                | Time from randomization to first SRE, defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain |
| Term                                      | Definition                                                                                       |
|-------------------------------------------|-------------------------------------------------------------------------------------------------|
| Time to initiation of cytotoxic chemotherapy | Time from randomization to initiation of cytotoxic chemotherapy                                |
| PSA response ≥50%                         | At least a 50% reduction in PSA from baseline to the lowest post-baseline PSA result, as determined by the central laboratory, with a consecutive assessment conducted at least 3 weeks later to confirm |
| Best overall soft-tissue response         | The best overall response was based on investigator assessment using RECIST, version 1.1, assessed in patients with measurable soft-tissue disease at the screening visit (at least one target lesion) who had an objective response (complete or partial) |

*ADT* androgen deprivation therapy, *CT* computed tomography, *GNRH* gonadotropin-releasing hormone, *MRI* magnetic resonance imaging, *OS* overall survival, *PCWG2* Prostate Cancer Clinical Trials Working Group 2, *PSA* prostate-specific antigen, *RECIST* Response Evaluation in Solid Tumors, *rPFS* radiographic progression-free survival, *SRE* skeletal-related event, *TTPP* time to PSA progression

*Progressive disease at study entry was defined by one or more of three criteria, which occurred while the patient was on ADT with a GnRH analog (agonist or antagonist) or bilateral orchietomy (i.e. surgical or medical castration) |

†Defined according to the consensus guidelines of the PCWG2 [1]
| Study center number | Institutional review board/ethics committee name |
|---------------------|--------------------------------------------------|
| China
102                | Shanghai Changhai Hospital Ethics Committee     |
103                | Ethics Committee of Beijing Hospital             |
104                | EC of Sun Yat-sen University Cancer Center       |
106                | Drug Clinical Trial Ethics Committee of Peking Union Medical College Hospital |
107                | EC of The First Affiliated Hospital of College of Medicine, Zhejiang University |
108                | Shanghai First People’s Hospital Ethics Committee |
109                | EC of Zhongnan Hospital of Wuhan University      |
110                | EC of The Affiliated Hospital of Nanjing University Medical School |
111                | Clinical Trial Ethics Committee of Peking University First Hospital |
112                | Drug Clinical Trial Ethics Committee of Beijing Friendship Hospital, Capital Medical University |
113                | Huashan Institutional Review Board (HIRB)        |
114                | Medical Scientific Research EC of Peking University Third Hospital |
115                | Ethics Committee of Beijing Cancer Hospital      |
117                | EC of Jiangsu Cancer Hospital                    |
118                | EC of The First Affiliated Hospital of Wenzhou Medical University |
119                | EC of The Second Affiliated Hospital of Soochow University |
120                | The First Affiliated Hospital of Nanjing Medical University Ethics Committee |
121                | IEC of Hunan Province Tumor Hospital             |
|   |Ethics Committee/Institution                               |
|---|----------------------------------------------------------|
|124| The First Affiliated Hospital of Xi’an Jiaotong University Ethics Committee |
|125| EC of the Second Hospital of Tianjin Medical University |
|126| IRB of Xinhua Hospital Affiliated to Shanghai Jiao Tong University, School of Medicine |
|127| Drug Clinical Trial Ethics Committee of The Affiliated Hospital of Academy of Military Medical Sciences |

### South Korea

|   | IRB of Institution                                      |
|---|---------------------------------------------------------|
|201| IRB of Gachon University Gil Hospital                   |
|202| IRB of Seoul National University Bundang Hospital        |
|203| IRB of Kyungpook National University Medical Center      |
|204| IRB of Samsung Medical Center                           |
|205| IRB of Inje University Busan Paik Hospital              |
|206| IRB of The Catholic University of Korea, Seoul St. Mary’s Hospital |
|207| IRB of Pusan National University Hospital               |
|208| IRB of Korea University Anam Hospital                   |
|209| IRB of Asan Medical Center                              |
|210| IRB of Seoul National University Hospital                |
|211| IRB of Severance Hospital                               |
|212| IRB of Chungbuk National University Hospital            |
|213| IRB of Chungnam National University Hospital            |
|214| IRB of Hallym University Sacred Heart Hospital          |
|215| IRB of Eulji General Hospital                           |

### Taiwan

|   | IRB of Institution                                     |
|---|---------------------------------------------------------|
|301| IRB of Taipei Veterans General Hospital                |
|302| IRB of Taichung Veterans General Hospital              |
| 303  | IRB of China Medical University Hospital |
| 304  | IRB of National Taiwan University Hospital |
| 305  | IRB of Chang Gung Medical Foundation – Linkou Branch |
| 306  | IRB of Tri-Service General Hospital-Neihu Main Facility |
| 307  | IRB of National Cheng Kung University Hospital |
| 308  | IRB of Chi Mei Medical Center |
| 309  | IRB of Kaohsiung Medical University Chung-Ho Memorial Hospital |

**Hong Kong**

| 402  | Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) |
Table S3 Patient demographics and baseline disease characteristics by country (intent-to-treat population)

| China                        | Enzalutamide (n = 102) | Placebo (n = 96) |
|------------------------------|-------------------------|------------------|
| Age, years, median (range)   | 70 (53–88)              | 72 (50–86)       |
| Age category, years, n (%)   |                         |                  |
| <65                          | 27 (26.5)               | 24 (25.0)        |
| 65–74                        | 42 (41.2)               | 36 (37.5)        |
| 75–84                        | 29 (28.4)               | 31 (32.3)        |
| ≥85                          | 4 (3.9)                 | 5 (5.2)          |
| BMI, kg/m², mean (± SD)      | 24.6 (± 3.1)            | 24.4 (± 3.0)     |
| Baseline ECOG performance status, n (%) |              |                  |
| 0                            | 46 (45.1)               | 61 (63.5)        |
| 1                            | 56 (54.9)               | 35 (36.5)        |
| BPI-SF, question 3 (worst pain in last 24 hours), n (%) | | |
| 0–1                          | 64 (62.7)               | 52 (54.2)        |
| 2–3                          | 38 (37.3)               | 44 (45.8)        |
| History of cardiovascular disease, n (%) | 5 (4.9)             | 8 (8.3)          |
| Baseline PSA, µg/L, median (range) | 115.4 (2.9–5000.0)    | 93.2 (3.0–2412.0) |

| Hong Kong                    | (n = 3)                | (n = 3)          |
|------------------------------|-------------------------|------------------|
| Age, years, median (range)   | 81 (68–84)              | 66 (61–83)       |
| Age category, years, n (%)   |                         |                  |
| <65                          | 0                       | 1 (33.3)         |
| Age category, years, n (%) | Korea (n = 51) | Japan (n = 49) |
|---------------------------|----------------|----------------|
| <65                       | 13 (25.5)      | 12 (24.5)      |
| 65–74                     | 18 (35.3)      | 19 (38.8)      |
| 75–84                     | 16 (31.4)      | 14 (28.6)      |
| ≥85                       | 4 (7.8)        | 4 (8.2)        |

| BMI, kg/m², mean (± SD)   | Korea          | Japan          |
|---------------------------|----------------|----------------|
|                           | 24.4 (± 3.2)   | 24.6 (± 3.1)   |

| Baseline ECOG performance status, n (%) | Korea | Japan |
|----------------------------------------|-------|-------|
| 0                                      | 32 (62.7) | 28 (57.1) |
| 1                                      | 19 (37.3)  | 21 (42.9)  |
|                          | Taiwan (n = 42) | (n = 42) |
|--------------------------|-----------------|----------|
| **BPI-SF, question 3 (worst pain in last 24 hours), n (%)** |                 |          |
| 0–1                      | 34 (66.7)       | 36 (73.5) |
| 2–3                      | 17 (33.3)       | 13 (26.5) |
| **History of cardiovascular disease, n (%)** | 3 (5.9) | 6 (12.2) |
| **Baseline PSA, µg/L, median (range)** | 39.0 (2.5–1503.5) | 33.6 (1.5–805.5) |

| **Taiwan**                | (n = 42)       | (n = 42)       |
|---------------------------|----------------|----------------|
| **Age, years, median (range)** | 73 (51–87)     | 71 (52–88)     |
| **Age category, years, n (%)** |                 |                |
| <65                       | 7 (16.7)       | 10 (23.8)      |
| 65–74                     | 20 (47.6)      | 17 (40.5)      |
| 75–84                     | 13 (31.0)      | 12 (28.6)      |
| ≥85                       | 2 (4.8)        | 3 (7.1)        |
| **BMI, kg/m², mean (± SD)** | 24.5 (± 2.9)  | 25.8 (± 3.5)  |
| **Baseline ECOG performance status, n (%)** |                 |                |
| 0                         | 33 (78.6)      | 32 (76.2)      |
| 1                         | 9 (21.4)       | 10 (23.8)      |
| **BPI-SF, question 3 (worst pain in last 24 hours), n (%)** |                 |                |
| 0–1                       | 36 (85.7)      | 34 (81.0)      |
| 2–3                       | 6 (14.3)       | 8 (19.0)       |
| **History of cardiovascular disease, n (%)** | 6 (14.3) | 3 (7.1) |
| **Baseline PSA, µg/L, median (range)** | 25.3 (3.0–461.2) | 59.8 (2.4–1383.0) |

*BMI* body mass index, *BPI-SF* Brief Pain Inventory–Short Form, *ECOG* Eastern Cooperative Oncology Group, *PSA* prostate-specific antigen, *SD* standard deviation
Table S4 Summary of treatments administered secondary to disease progression (intent-to-treat population)

| Therapeutic subgroup (ATC 2nd level) | Enzalutamide ($n = 198$) | Placebo ($n = 190$) |
|-------------------------------------|--------------------------|---------------------|
| **Antineoplastic agents**           |                          |                     |
| Other antineoplastic agents         | 1 (0.5)                  | 1 (0.5)             |
| Celecoxib                           | 0                        | 1 (0.5)             |
| Estramustine phosphate              | 0                        | 1 (0.5)             |
| Taxanes                             | 1 (0.5)                  | 0                   |
| Docetaxel                           | 1 (0.5)                  | 0                   |
| **Endocrine therapy**               | 162 (81.8)               | 142 (74.7)          |
| Antiandrogens                       | 2 (1.0)                  | 5 (2.6)             |
| Bicalutamide                        | 1 (0.5)                  | 4 (2.1)             |
| Flutamide                           | 1 (0.5)                  | 1 (0.5)             |
| Estrogens                           | 0                        | 1 (0.5)             |
| Ethinylestradiol                    | 0                        | 1 (0.5)             |
| Gonadotropin-releasing hormone analogs | 162 (81.8)           | 140 (73.7)          |
| Goserelin                           | 45 (22.7)                | 43 (22.6)           |
| Goserelin acetate                   | 19 (9.6)                 | 11 (5.8)            |
| Leuprolelin                         | 37 (18.7)                | 33 (17.4)           |
| Leuprolelin acetate                 | 50 (25.3)                | 45 (23.7)           |
| Triptorelin                         | 14 (7.1)                 | 8 (4.2)             |
| Triptorelin acetate                 | 6 (3.0)                  | 6 (3.2)             |
| Medication                          | Count | Percentage |
|-----------------------------------|-------|------------|
| Triptorelin embonate              | 2 (1.0) | 0          |
| Other hormone antagonists and related agents | 0 | 2 (1.1)   |
| Abiraterone                       | 0     | 2 (1.1)    |
| **Sex hormones**                  |       |            |
| Antiandrogens, plain              | 0     | 1 (0.5)    |
| Cyproterone acetate               | 0     | 1 (0.5)    |

ATC anatomical therapeutic chemical, PSA prostate-specific antigen, WHO World Health Organization

A subject may have taken more than one medication; therefore, the sum of medication counts and percentages may not equal the total counts. Hormonal therapies including other antiandrogens and biological antitumor treatments were permitted only once the patient had centrally confirmed radiographic progression and centrally confirmed PSA progression.
| Table S5 Exploratory endpoints: assessments of QoL (intent-to-treat population) |
|-------------------------------------------------|-----------------|-----------------|
| | **Enzalutamide** *(n = 198)* | **Placebo** *(n = 190)* |
| **Time to degradation of FACT-P**<sup>•</sup> | | |
| Patients with degradation of FACT-P, *n* (%) | 9 (4.5) | 7 (3.7) |
| Median time to degradation of FACT-P, months (range) | NYR (0.0–14.0) | NYR (0.0–11.1) |
| *P* value | 0.54 | |
| HR (95% CI) | 0.73 (0.27–1.99) | |
| **EQ-5D health state score, mean (± SD)**<sup>†</sup> | | |
| Baseline | 74.8 (± 16.0) | 76.6 (± 15.9) |
| Week 13 | 77.9 (± 14.3) | 76.3 (± 17.0) |
| Week 25 | 77.2 (± 14.2) | 75.1 (± 15.5) |
| Week 37 | 77.2 (± 15.2) | 76.7 (± 17.6) |
| Week 49 | 76.5 (± 17.7) | 71.2 (± 28.7) |
| **BPI-SF** | | |
| Pain intensity score at baseline, mean (± SD)<sup>‡</sup> | 0.61 (± 0.91) | 0.63 (± 0.92) |
| Pain intensity score at Month 3, mean (± SD) | 0.55 (± 1.09) | 0.87 (± 1.34) |
| *n* | 174 | 130 |
| Pain intensity score at Month 6, mean (± SD) | 0.60 (± 1.15) | 0.93 (± 1.60) |
| *n* | 120 | 55 |
| Pain progression<sup>§</sup> | 27 (22.5%) | 17 (30.9%) |
| *n* | 120 | 55 |
| Difference in pain progression (95% CI) | −8.4% (−22.7 to 5.9) | |
| *P* value | 0.26 | |
*Degradation of FACT-P defined as ≥10-point decrease from baseline in global score and ≥3-point decrease from baseline in each subscale

†Visual analog scale from 0 (worst imaginable health state) to 100 (best imaginable health state)

‡Mean pain intensity score defined as average of BPI pain intensity item scores (items 3–6)

§Pain progression defined as an increase of ≥30% from baseline in mean pain intensity score at Month 6
Table S6 SAEs leading to death by system organ class and preferred term at the primary analysis (safety population)

| n (%)* | Enzalutamide (n = 198) | Placebo (n = 190) |
|--------|------------------------|-------------------|
| Total patients with SAEs leading to death | 7 (3.5) | 6 (3.2) |
| Infections and infestations | 2 (1.0) | 1 (0.5) |
| Pneumonia | 1 (0.5) | 0 |
| Septic shock | 1 (0.5) | 1 (0.5) |
| General disorders/administration site conditions | 0 | 3 (1.6) |
| Death† | 0 | 2 (1.1) |
| Multiorgan failure | 0 | 1 (0.5) |
| Respiratory, thoracic, and mediastinal disorders | 1 (0.5) | 2 (1.1) |
| Respiratory failure | 0 | 2 (1.1) |
| Pulmonary embolism | 1 (0.5) | 0 |
| Cardiac disorders | 2 (1.0) | 0 |
| Cardiac failure | 1 (0.5) | 0 |
| Cardiopulmonary failure | 1 (0.5) | 0 |
| Metabolism and nutrition disorders | 1 (0.5) | 0 |
| Cachexia | 1 (0.5) | 0 |
| Musculoskeletal and connective-tissue disorders | 1 (0.5) | 0 |
| Bone pain | 1 (0.5) | 0 |

AE adverse event, SAE serious adverse event

*Percentage of patients reporting at least one AE within the specified system organ class

†Reported as ‘Death (reason unknown)’
Table S7 Overview of AEs at 5-year analysis (safety population)*

| n (%)                      | Enzalutamide (n = 202) | Placebo (n = 193) | Placebo crossover (n = 51) |
|----------------------------|-------------------------|-------------------|---------------------------|
| AEs                        | 190 (94.1)              | 166 (86.0)        | 47 (92.2)                 |
| AEs leading to study drug discontinuation | 49 (24.3)              | 42 (21.8)        | 12 (23.5)                 |
| Drug-related AEs †         | 102 (50.5)              | 59 (30.6)        | 13 (25.5)                 |
| Grade 3 or higher AEs      | 97 (48.0)               | 66 (34.2)        | 27 (52.9)                 |
| SAEs                       | 86 (42.6)               | 57 (29.5)        | 23 (45.1)                 |
| Drug-related SAEs          | 13 (6.4)                | 7 (3.6)          | 3 (5.9)                   |
| SAEs leading to death      | 24 (11.9)               | 7 (3.6)          | 7 (13.7)                  |
| Drug-related SAEs leading to death | 2 (1.0)               | 0                | 1 (2.0)                   |

AE adverse event, SAE serious adverse event

*AEs were recorded in the electronic case report form and graded based on the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0, by the study investigators

†Drug-related AEs were defined as AEs with a possible or probable relationship to the study drug, as determined by investigators
Table S8 Most common any grade and ≥3 AEs at 5-year analysis by system organ class and preferred term (safety population)

|                      | Enzalutamide (n = 202) | Placebo (n = 193) | Placebo crossover (n = 51) |
|----------------------|-------------------------|-------------------|---------------------------|
| **n (%)**            |                         |                   |                           |
| Musculoskeletal and connective tissue disorders |                         |                   |                           |
| Back pain            | 37 (18.3)               | 20 (10.4)         | 6 (11.8)                  |
| Arthralgia           | 26 (12.9)               | 12 (6.2)          | 1 (2.0)                   |
| Pain in extremity    | 25 (12.4)               | 18 (9.3)          | 0                         |
| Bone pain            | 19 (9.4)                | 25 (13.0)         | 2 (3.9)                   |
| Musculoskeletal pain | 14 (6.9)                | 5 (2.6)           | 1 (2.0)                   |
| Gastrointestinal disorders | 87 (43.1)   | 58 (30.1)         | 16 (31.4)                 |
| Constipation         | 26 (12.9)               | 15 (7.8)          | 3 (5.9)                   |
| Nausea               | 23 (11.4)               | 11 (5.7)          | 4 (7.8)                   |
| Vomiting             | 11 (5.4)                | 7 (3.6)           | 2 (3.9)                   |
| Abdominal pain       | 10 (5.0)                | 4 (2.1)           | 2 (3.9)                   |
| Diarrhea             | 8 (4.0)                 | 5 (2.6)           | 4 (7.8)                   |
| General disorders/administration site conditions | 76 (37.6)   | 48 (24.9)         | 9 (17.6)                  |
| Fatigue              | 29 (14.4)               | 15 (7.8)          | 3 (5.9)                   |
| Peripheral edema     | 14 (6.9)                | 7 (3.6)           | 4 (7.8)                   |
| Asthenia             | 13 (6.4)                | 8 (4.1)           | 2 (3.9)                   |
| Pyrexia              | 11 (5.4)                | 12 (6.2)          | 1 (2.0)                   |
| Diagnosis                                              | Count | Percent | Median | Mode |
|--------------------------------------------------------|-------|---------|--------|------|
| Infections and infestations                            | 75 (37.1) | 31 (16.1) | 17 (33.3) | |
| Nasopharyngitis                                        | 21 (10.4) | 7 (3.6) | 3 (5.9) | |
| Upper respiratory tract infection                      | 13 (6.4) | 7 (3.6) | 5 (9.8) | |
| Lung infection                                         | 12 (5.9) | 3 (1.6) | 1 (2.0) | |
| Periodontitis                                          | 5 (2.5) | 1 (0.5) | 3 (5.9) | |
| Investigations                                         | 61 (30.2) | 31 (16.1) | 10 (19.6) | |
| Decreased weight                                       | 23 (11.4) | 11 (5.7) | 5 (9.8) | |
| Nervous system disorders                               | 56 (27.7) | 24 (12.4) | 11 (21.6) | |
| Dizziness                                              | 22 (10.9) | 8 (4.1) | 3 (5.9) | |
| Renal and urinary disorders                            | 50 (24.8) | 32 (16.6) | 7 (13.7) | |
| Dysuria                                                | 17 (8.4) | 8 (4.1) | 1 (2.0) | |
| Hematuria                                              | 17 (8.4) | 13 (6.7) | 0 | |
| Pollakiuria                                            | 13 (6.4) | 2 (1.0) | 1 (2.0) | |
| Hydronephrosis                                         | 5 (2.5) | 1 (0.5) | 3 (5.9) | |
| Metabolism and nutrition disorders                     | 58 (28.7) | 26 (13.5) | 11 (21.6) | |
| Decreased appetite                                     | 38 (18.8) | 19 (9.8) | 6 (11.8) | |
| Hyperglycemia                                          | 10 (5.0) | 1 (0.5) | 0 | |
| Blood and lymphatic system disorders                   | 36 (17.8) | 19 (9.8) | 8 (15.7) | |
| Anemia                                                 | 32 (15.8) | 18 (9.3) | 8 (15.7) | |
| Vascular disorders                                     | 34 (16.8) | 9 (4.7) | 3 (5.9) | |
| Hypertension                                           | 20 (9.9) | 2 (1.0) | 2 (3.9) | |
| Respiratory, thoracic, and mediastinal disorders       | 29 (14.4) | 18 (9.3) | 9 (17.6) | |
| Cough                                                  | 9 (4.5) | 7 (3.6) | 5 (9.8) | |
| Psychiatric disorders                                  | 20 (9.9) | 7 (3.6) | 0 | |
| Category                                      | Count (Prevalence) | Count (Prevalence) | Count (Prevalence) |
|-----------------------------------------------|--------------------|--------------------|--------------------|
| Insomnia                                      | 17 (8.4)           | 5 (2.6)            | 0                  |
| Eye disorders                                 | 16 (7.9)           | 9 (4.7)            | 6 (11.8)           |
| Cataract                                      | 6 (3.0)            | 1 (0.5)            | 4 (7.8)            |
| **AEs of grade ≥3 occurring in ≥2% of patients in any treatment group** |                    |                    |                    |
| Infections and infestations                   | 22 (10.9)          | 7 (3.6)            | 7 (13.7)           |
| Lung infection                                | 10 (5.0)           | 1 (0.5)            | 1 (2.0)            |
| Musculoskeletal and connective tissue disorders| 12 (5.9)           | 16 (8.3)           | 6 (11.8)           |
| Back pain                                     | 1 (0.5)            | 2 (1.0)            | 2 (3.9)            |
| Bone pain                                     | 5 (2.5)            | 8 (4.1)            | 1 (2.0)            |
| Investigations                                | 16 (7.9)           | 11 (5.7)           | 4 (7.8)            |
| Weight decreased                              | 4 (2.0)            | 0                  | 4 (7.8)            |
| Renal and urinary disorders                   | 19 (9.4)           | 11 (5.7)           | 3 (5.9)            |
| Hematuria                                     | 5 (2.5)            | 5 (2.6)            | 0                  |
| Hydronephrosis                                | 2 (1.0)            | 1 (0.5)            | 2 (3.9)            |
| Blood and lymphatic system disorders          | 14 (6.9)           | 8 (4.1)            | 5 (9.8)            |
| Anemia                                        | 11 (5.4)           | 7 (3.6)            | 5 (9.8)            |
| Nervous system disorders                      | 10 (5.0)           | 3 (1.6)            | 6 (11.8)           |
| Dizziness                                     | 2 (1.0)            | 0                  | 1 (2.0)            |
| Gastrointestinal disorders                    | 10 (5.0)           | 4 (2.1)            | 2 (3.9)            |
| Nausea                                        | 0                  | 0                  | 1 (2.0)            |
| Vomiting                                      | 0                  | 0                  | 1 (2.0)            |
| Abdominal pain                                | 0                  | 0                  | 1 (2.0)            |
| General disorders/administration site conditions | 8 (4.0)           | 8 (4.1)            | 1 (2.0)            |
| System Organ Class                                      | Number (Percentage) | Number (%) | Number (%) |
|--------------------------------------------------------|---------------------|------------|------------|
| Metabolism and nutrition disorders                      | 12 (5.9)            | 3 (1.6)    | 1 (2.0)    |
| Decreased appetite                                      | 5 (2.5)             | 1 (0.5)    | 0          |
| Respiratory, thoracic, and mediastinal disorders        | 6 (3.0)             | 6 (3.1)    | 1 (2.0)    |
| Vascular disorders                                      | 10 (5.0)            | 2 (1.0)    | 1 (2.0)    |
| Hypertension                                            | 7 (3.5)             | 0          | 0          |
| Eye disorders                                            | 5 (2.5)             | 1 (0.5)    | 2 (3.9)    |
| Cataract                                                | 3 (1.5)             | 0          | 2 (3.9)    |

*AE adverse event*

*Percentage of patients reporting at least one AE within the specified system organ class*
Table S9 Comparison of PREVAIL Asia and PREVAIL studies [2, 3]

|                      | PREVAIL Asia |          | PREVAIL |          |
|----------------------|--------------|----------|----------|----------|
|                      | Enzalutamide | Placebo | Enzalutamide | Placebo |
|                      | \( n = 198 \) | \( n = 190 \) | \( n = 872 \) | \( n = 845 \) |
| Demographics and clinical characteristics | | | | |
| Age, years, median (range) | 71 (51–89) | 71 (50–88) | 72 (43–93) | 71 (42–93) |
| Baseline ECOG performance status = 1, \( n (%) \) | 85 (42.9) | 66 (34.7) | 288 (33.0) | 260 (30.8) |
| Gleason score \( \geq 8 \), \( n (%) \) | 138 (69.7) | 117 (61.6) | 424 (50.6) | 423 (52.4) |
| Number of bone metastases at screening, \( n (%) \) | | | | |
| 0                    | 0            | 0        | 131 (15.0) | 155 (18.3) |
| 1–9                  | 111 (56.1)   | 100 (52.6) | 456 (52.2) | 418 (49.5) |
| 10–20                | 43 (21.7)    | 45 (23.7) | 140 (16.1) | 122 (14.4) |
| >20                  | 32 (16.2)    | 31 (16.3) | 145 (16.6) | 150 (17.8) |
| Efficacy endpoints (primary analysis) [3] | | | | |
| Median TTPP, months | 8.3          | 2.9      | 11.2     | 2.8      |
| HR (95% CI)          | 0.38 (0.27–0.52) | 0.17 (0.15–0.20) | | |
| \( P \) value        | \( P < 0.0001 \) | \( P < 0.001 \) | | |
| Median rPFS events, months | NYR | 5.3 | NYR | 3.9 |
| HR (95% CI)          | 0.31 (0.20–0.46) | 0.19 (0.15–0.23) | | |
| \( P \) value        | \( P < 0.0001 \) | \( P < 0.001 \) | | |
| Safety (primary analysis) | \( n = 871 \) | \( n = 844 \) | | |
| Any-grade AEs, \( n (%) \) | 167 (84.3) | 153 (80.5) | 844 (97) | 787 (93) |
|                                                                 | n (%)  | n (%)  | n (%)  | n (%)  |
|-----------------------------------------------------------------|--------|--------|--------|--------|
| Grade ≥3 AEs, n (%)                                             | 49 (24.7) | 56 (29.5) | 374 (43) | 313 (37) |
| SAEs, n (%)                                                     | 34 (17.2) | 47 (24.7) | 279 (32) | 226 (27) |
| AEs leading to treatment discontinuation, n (%)                 | 26 (13.1) | 34 (17.9) | 49 (6) | 51 (6) |
| **5-year analysis [2]**                                         |        |        |        |        |
| Median OS, months                                              | 39.1   | 27.1   | 36     | 31     |
| HR (95% CI)                                                    | 0.70 (0.51–0.95) | 0.83 (0.75–0.93) |        |        |
| P value                                                        | $P = 0.0208$ | $P < 0.001$ |        |        |
| Patients with subsequent antineoplastic treatment, n (%)       | 36 (17.8) | 55 (28.5) | 610 (70) | 725 (85.8) |
| Any grade AEs, n (%)                                           | 190 (94.1) | 166 (86.0) | 857 (98) | 791 (94) |
| Grade ≥3 AEs, n (%)                                            | 97 (48.0) | 66 (34.2) | 462 (53) | 318 (38) |
| SAEs, n (%)                                                     | 86 (42.6) | 57 (29.5) | 382 (44) | 229 (27) |
| AEs leading to treatment discontinuation, n (%)                 | 49 (24.3) | 42 (21.8) | 79 (9.1) | 51 (6.0) |

AE adverse event, CI confidence interval, ECOG Eastern Cooperative Oncology Group, HR hazard ratio, OS overall survival, rPFS radiographic progression-free survival, SAE serious adverse event, TTPP time to PSA progression
References

1. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26:1148–59.

2. Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua AM, 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;78:347–57.

3. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–33.
Fig. S1 Patient disposition. AE adverse event

Enrolled
\( n = 388 \)

Randomized

Discontinued treatment
\( n = 62 \)
Disease progression \( n = 23 \)
Withdrawn consent \( n = 14 \)
Other \( n = 11 \)
AE \( n = 11 \)
Death \( n = 3 \)

Discontinued long-term follow-up
\( n = 34 \)
Death \( n = 11 \)
Withdrawn consent \( n = 22 \)
Other \( n = 1 \)

Enzalutamide
\( n = 198 \)

Placebo
\( n = 190 \)

Discontinued treatment
\( n = 131 \)
Disease progression \( n = 39 \)
Withdrawn consent \( n = 45 \)
Other \( n = 32 \)
AE \( n = 10 \)
Death \( n = 3 \)
Protocol violation \( n = 2 \)

Treatment ongoing
\( n = 136 \)

Treatment ongoing
\( n = 59 \)

Discontinued long-term follow-up
\( n = 80 \)
Death \( n = 21 \)
Withdrawn consent \( n = 53 \)
Other \( n = 6 \)
Fig. S2 Kaplan–Meier curves for OS at the primary analysis (intent-to-treat population). CI confidence interval, HR hazard ratio, OS overall survival
**Fig. S3** Subgroup analysis of OS at 5-year analysis (intent-to-treat population). *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *HR* hazard ratio, *LDH* lactate dehydrogenase, *NR* not reached, *OS* overall survival, *PSA* prostate-specific antigen

| Subgroup                                                   | Number of patients | Median (months) | HR (95% CI) |
|------------------------------------------------------------|--------------------|-----------------|-------------|
| All subgroups                                              | Enzalutamide       | Placebo         | Enzalutamide | Placebo |                |
| ECOG performance status = 0 at baseline                    | 202                | 183             | 39.1        | 27.1    | 0.70 (0.51–0.95) |
| ECOG performance status = 1 at baseline                    | 113                | 126             | 52.0        | 37.8    | 0.81 (0.54–1.23) |
| Age category <75 years                                     | 89                 | 67              | 31.8        | 15.5    | 0.40 (0.25–0.65) |
| Age category ≥75 years                                     | 128                | 122             | 44.4        | 37.0    | 0.71 (0.47–1.07) |
| Country or region: China                                   | 106                | 99              | 24.9        | 21.8    | 0.70 (0.44–1.10) |
| Country or region: Korea                                   | 51                 | 49              | NR          | NR      | 0.81 (0.07–9.72) |
| Country or region: Taiwan                                 | 42                 | 42              | 50.2        | 29.8    | 0.82 (0.43–1.55) |
| Country or region: Hong Kong                               | 3                  | 3               | 45.1        | 47.3    | 2.92 (2.26–32.9) |
| Total Gleason score ≤7 at diagnosis                        | 57                 | 64              | 34.6        | 42.1    | 1.07 (0.60–1.91) |
| Total Gleason score >8 at diagnosis                        | 141                | 119             | 39.8        | 22.9    | 0.52 (0.36–0.76) |
| Type of progression at study entry: PSA progression only   | 137                | 126             | 52.0        | 30.5    | 0.61 (0.41–0.89) |
| Type of progression at study entry: radiographic progression with or without PSA progression | 65                 | 67              | 29.8        | 25.0    | 0.94 (0.56–1.57) |
| Visceral disease at screening                              | 25                 | 17              | 19.6        | 8.7     | 0.38 (0.17–0.85) |
| No visceral disease at screening                            | 177                | 176             | 44.4        | 31.7    | 0.72 (0.52–1.01) |
| Prior androgen use                                         | 174                | 174             | 34.8        | 25.9    | 0.73 (0.53–1.00) |
| No prior androgen use                                      | 28                 | 19              | NR          | NR      | 0.55 (0.18–1.66) |
| Baseline bisphosphonate or denosumab use                   | 46                 | 48              | 30.7        | 19.4    | 0.62 (0.35–1.09) |
| No baseline bisphosphonate or denosumab use                | 156                | 145             | 44.6        | 31.7    | 0.74 (0.51–1.07) |
| Baseline PSA value at or below median                       | 103                | 95              | 59.2        | 42.1    | 0.77 (0.46–1.29) |
| Baseline PSA value above median                             | 99                 | 98              | 25.3        | 19.4    | 0.68 (0.46–1.00) |
| Baseline LDH value at or below median                       | 104                | 95              | NR          | 41.7    | 0.68 (0.43–1.09) |
| Baseline LDH value above median                             | 98                 | 98              | 27.0        | 15.4    | 0.67 (0.45–1.01) |
| Baseline hemoglobin value at or below median                | 110                | 97              | 29.7        | 19.1    | 0.50 (0.34–0.75) |
| Baseline hemoglobin value above median                      | 92                 | 96              | 50.2        | 45.7    | 0.89 (0.55–1.46) |