Comparison of standard-dose and reduced-dose treatment of metastatic prostate cancer with enzalutamide, apalutamide or darolutamide: a rapid review

Hannah Louise Bromley, Mohini Varughese, Duncan C Gilbert, Peter Hoskin, Ian F Tannock, Kimberley Reeves, Ananya Choudhury

ABSTRACT
Objective To review the efficacy and safety of low-dose versus standard-dose enzalutamide, apalutamide or darolutamide treatment for metastatic prostate cancer.

Methods and analysis Keyword searches in MEDLINE and EMBASE up to 1 June 2023, with forward and backward citation searches of potentially relevant studies. Studies were included if primary outcome data were reported for patients with metastatic prostate cancer who had received reduced doses of enzalutamide, apalutamide or darolutamide. Searches were limited to original full-text and English-language studies. Key outcomes included overall survival (OS), progression-free survival (PFS), prostate-specific antigen response and treatment-related adverse events. The review was performed in accordance with Cochrane Rapid Reviews Methods Group guidelines.

Results Ten studies were identified that met the eligibility criteria: five phase I studies, two post-hoc analyses of phase III trials and three retrospective analyses. No consistent association between OS, PFS and drug dose was identified. Fewer severe treatment-related adverse events were observed at lower drug doses.

Conclusion This review provides evidence that enzalutamide, apalutamide or darolutamide could be given at a lower than the standard recommended dose without loss of antitumour activity. A prospective near-equivalence randomised trial should be undertaken to compare registered and lower doses of these agents.

PROSPERO registration number CRD42023440371.

INTRODUCTION
Enzalutamide, apalutamide and darolutamide are androgen receptor (AR) inhibitors which improve overall survival (OS) of men with metastatic prostate cancer, when added to standard androgen deprivation therapy (ADT) in randomised controlled trials (RCTs). The recommended doses of enzalutamide (160mg/day), apalutamide (240mg/day) and darolutamide (1200mg/day) were established in phase I trials. Enzalutamide improves OS in men with castrate-resistant prostate cancer (CRPC) before and after docetaxel chemotherapy, and in metastatic hormone-sensitive prostate cancer (MHSPC). Apalutamide and darolutamide demonstrated increased OS in men with MHSPC. All three drugs also improve metastasis-free survival in men with non-metastatic CRPC and a rapidly rising prostate-specific antigen (PSA).

Although effective and relatively well tolerated compared with other anticancer drugs, each of the ‘utamides has associated toxicities and in practice, lower doses may be prescribed in elderly patients or those with comorbidity or poor performance status. Enzalutamide increases fatigue, which may improve with dose reduction. Apalutamide can cause a skin rash or other dermatological side-effects, including pruritus, in about one
in four men,2,15 requiring either treatment interruption or dose reduction. There are claims that darolutamide is less toxic, and that it does not cross the blood–brain barrier, although there is no robust clinical evidence to support this claim.16 All three drugs increase the risk of cardiovascular events and hypertension.17

This rapid review summarises outcomes of men with metastatic prostate cancer, treated with enzalutamide, apalutamide or darolutamide at a lower than the recommended dose.

METHODS

Study design
This study adopted guidelines from the Cochrane Rapid Reviews Methods Group.18 Rapid reviews enable an efficient and pragmatic approach to evidence synthesis, in which key components of a systematic review are simplified,19 allowing a clinical question to be addressed rapidly. The study protocol was registered on PROSPERO (ID number: CRD42023440371), to promote reproducibility and methodological transparency.20

Search strategy
Keyword searches together with Boolean operators (OR±AND) and truncation (*) were conducted to identify English-language peer-reviewed literature, related to standard and lower-dose enzalutamide, apalutamide and darolutamide treatment of men with metastatic prostate cancer.

MEDLINE and EMBASE electronic databases were searched for studies published up to 1 April 2023 and updated on 1 June 2023. Studies were limited to original full-text and English-language records. Keyword searches included “prostat* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)” OR “prostate cancer/” AND “Androgen Antagonists/” OR (enzalutamide or apalutamide or darolutamide”) AND “dos* OR Dose-Response Relationship, Drug/ OR Drug dose regimen/”.

Study selection
All retrieved studies were collated and managed via EndNote referencing software.21 A two-stage process was used to identify relevant studies for inclusion in the final review.18 First, the title and abstracts were screened against the eligibility criteria, and then the full text of possible relevant studies was assessed for relevance. The reference lists of potentially relevant studies were also searched. Studies reporting primary outcomes which met the eligibility criteria were included in the final review. A second reviewer checked a sample of studies to investigate any selection bias, and disagreements were resolved through discussion.

Eligibility criteria
Studies were included if they met the following inclusion criteria:

► Population: adult men (aged >18 years) with a diagnosis of metastatic prostate cancer.
► Intervention: reduced doses of enzalutamide, apalutamide or darolutamide.
► Comparator: recommended doses of enzalutamide, apalutamide or darolutamide.
► Outcomes: any primary data reported on progression-free survival (PFS), OS, toxicity or adverse effects, PSA response, duration of treatment, health-related quality of life.
► Type: English language, primary/original full-text studies.

Systematic reviews, editorials, commentaries, opinion pieces and meeting abstracts were excluded.

Data analysis
An electronic template adapted from the Cochrane Review Methods Group18 was used to extract data on the characteristics and outcomes from the included studies. Data on study methods, participants, doses, clinical outcomes and adverse events were tabulated and the results analysed narratively. Due to the heterogeneity of study designs, patient characteristics, drug doses and outcomes, a formal meta-analysis was considered statistically inappropriate (online supplemental file 1).

A formal quality appraisal was not performed due to the scoping nature of the review and range of different study types included.

RESULTS

Search results
A total of 1302 citations were identified in the literature search, of which 143 were removed as duplicates. Ten studies were included in the final review. Figure 1 summarises the studies included and excluded at each stage of the literature search.

Study characteristics
A summary of the included studies, design and outcomes is provided in table 1. Evidence pertaining to clinical outcomes from reduced-dose enzalutamide, apalutamide and darolutamide is from phase I studies, post-hoc analyses of phase III trials and retrospective cohort analyses.

Phase I trials
Five phase I studies generated data on the clinical effectiveness of enzalutamide, apalutamide and darolutamide at lower doses.3,7,8,22,23

In the original phase I study of enzalutamide (formerly MDV3100),3 140 men were treated with doses between 30 and 600 mg/day. Antitumour effects were observed at all doses, including decreases in serum PSA of ≥50% in over half of all patients. There was an almost linear increase in steady-state serum concentration with dose, but no trends to increased target binding or tumour response at doses from 60 mg to 360 mg/day. The registered dose is 160 mg/day. An increase in the severity of
treatment-related adverse effects was associated with drug dose; grade 3–4 fatigue was associated with higher doses (≥240 mg/day). Symptoms generally resolved after dose reduction. A similar pharmacokinetic profile was observed in a Japanese phase I/II multicentre study of enzalutamide in patients with metastatic CRPC (n=9 in phase I, n=38 in phase II). Pharmacokinetic profiles were dose proportional at doses from 80 to 240 mg/day. Fewer serious treatment-emergent adverse events were reported at lower doses of <160 mg/day. PSA reduction from baseline was observed at 160 mg/day in the phase II study, but data on antitumour activity were not reported for the lower doses in phase I.

In phase I trials of apalutamide (formerly ARN-509), 30 patients received doses from 30 to 480 mg/day. Pharmacokinetics were linear and dose proportional. Antitumour activity was observed at all doses with a plateau effect ≥120 mg/day and >90% inhibition of testosterone binding to the AR in FDHT/positron emission tomography CT analysis. The registered dose is 240 mg/day. In a phase I/II study of darolutamide (formerly ODM-201), 110 men with metastatic CRPC were randomised to receive 200, 400 or 1400 mg/day. Exposure at steady state increased in a linear, dose-related manner up to 1400 mg/day. PSA response at 12 weeks was similar at these doses (29%, 33% and 33%), although in men without prior treatment with abiraterone or similar agent, the 200 mg...
No difference in adverse events was observed between groups when examined by dose or by previous treatment.8 Extended follow-up of 77 patients from the phase I/II trial of darolutamide was undertaken among individuals

<table>
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<tr>
<th>Study</th>
<th>Drug and dose</th>
<th>Population</th>
<th>Methods and design</th>
<th>Adverse events (AEs)</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akaza et al26</td>
<td>Enzalutamide 80–240 mg</td>
<td>MCRPC</td>
<td>Multicentre open-label phase I/II trial in Japan; phase I (n=88), phase II (n=38) patients</td>
<td>Fewer AEs in phase I at low dose (22.2% vs 34.2%)</td>
<td>Pharmacokinetics dose proportional from 80 to 240 mg</td>
</tr>
<tr>
<td>Fizazi et al8</td>
<td>Darolutamide 200–1800 mg</td>
<td>MCRPC</td>
<td>Multicentre open-label uncontrolled phase I/Ii in Europe and the USA (n=124)</td>
<td>Most common AEs were fatigue (12%) or hot flushes (5%); no differences observed by dose</td>
<td>Phase I: no dose-limiting toxic effects, maximum tolerated dose not reached. Phase II: 11 (29%) patients in 200 mg, 13 (33%) in 400 mg and 11 (33%) in 1400 mg groups achieved PSA response at 12 weeks</td>
</tr>
<tr>
<td>Fizazi et al23</td>
<td>Darolutamide 200–1800 mg</td>
<td>MCRPC</td>
<td>Extended follow-up of multicentre phase I/Ii in CYP17 inhibitor-naive patients (n=77)</td>
<td>The most common AEs: fatigue, diarrhoea, anorexia, hot flushes</td>
<td>PSA progression, HR 0.47 (95% CI 0.12 to 1.82; p=0.2743) for 1400 mg group and 1.32 (95% CI 0.48 to 3.62; p=0.596) for the 400 mg group compared with the 200 mg/day group</td>
</tr>
<tr>
<td>Freedland et al26</td>
<td>Enzalutamide reduced dose (&lt;80%)</td>
<td>MCRPC</td>
<td>Retrospective longitudinal cohort study of US veteran health data (n=6069)</td>
<td>No AE reported</td>
<td>RDI &lt;80% associated with higher-risk PSA progression, HR 1.258 (95% CI 1.080 to 1.464, p&lt;0.003); no assessment of PFS or OS</td>
</tr>
<tr>
<td>Oishi et al27</td>
<td>Apalutamide 240 mg or reduced dose (60–180 mg/day)</td>
<td>MCSPC</td>
<td>Multicentre retrospective study (53 non-MCRPC and 72 MCRPC)</td>
<td>No difference in skin AE between doses (p=0.761)</td>
<td>No difference in skin-related AE-free survival between dose groups (p=0.33) No difference in CRPC-free survival between doses in metastatic disease (p=0.525) Drug discontinuation higher in standard (50%) versus reduced dose (16.7%) (p=0.021)</td>
</tr>
<tr>
<td>Rathkopf et al7</td>
<td>Apalutamide 30–480 mg/day</td>
<td>MCRPC</td>
<td>Phase I study in single centre at doses between 30 mg and 480 mg (n=30)</td>
<td>Most common AE was fatigue</td>
<td>Pharmacokinetics linear and dose proportional. Dose escalation to 480 mg did not identify a maximum tolerated dose. Reduced FDHT uptake at all doses, with a plateau in response at ≥240 mg</td>
</tr>
<tr>
<td>Scher et al5</td>
<td>Enzalutamide 30–600 mg</td>
<td>MCRPC</td>
<td>Phase I/Ii study undertaken in the USA (n=140)</td>
<td>Severe fatigue dose dependent. Fatigue highest in doses ≥240 mg/day</td>
<td>Antitumour effects were observed at all doses. Maximum tolerated dose for sustained treatment was 240 mg</td>
</tr>
<tr>
<td>T’jollyn et al28</td>
<td>Apalutamide 240 mg: quartiles of dose exposure</td>
<td>MCSPC</td>
<td>Retrospective analysis of phase III randomised controlled trial (n=1052), comparing quartiles of dose exposure</td>
<td>Skin rash and pruritus increased with increasing apalutamide exposure</td>
<td>No statistical association between OS and apalutamide exposure quartiles No association detected between radiographic PFS and apalutamide exposure quartiles</td>
</tr>
<tr>
<td>Vinh-Hung et al24</td>
<td>Enzalutamide 160 mg/day vs ≤80 mg/day</td>
<td>Metastatic prostate cancer (n=111)</td>
<td>Retrospective review at a single centre in the Caribbean</td>
<td>Limited data reported</td>
<td>No difference in OS and PFS between low dose and standard dose groups Better longevity in low dose group, RMAA 85.1 years vs 63.8 years (p=0.003)</td>
</tr>
<tr>
<td>Vinh-Hung et al25</td>
<td>Enzalutamide 160 mg/day vs ≤80 mg/day</td>
<td>Metastatic prostate cancer</td>
<td>Retrospective review of men aged ≥75 years at a single centre in the Caribbean (n=59)</td>
<td>No AEs reported in low dose group</td>
<td>PSA decrease ≥50% at 12 weeks in 67% with low dose vs 45% with standard dose (p=0.152) Median PFS 11.2 months in low dose group vs 11.9 months for standard dose (p=0.012)</td>
</tr>
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</table>

CRPC, castrate-resistant prostate cancer; FDHT, Fluorodihydrotestosterone; MCRPC, metastatic CRPC; MCSPC, metastatic castrate-sensitive prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; RDI, relative dose intensity; RMAA, restricted mean attained age.

dose was inferior; there was no difference between 400 and 1400 mg/day. The registered dose is 1200 mg/day. No difference in adverse events was observed between...
with CYP17 inhibitor-naïve CRPC. Antitumour activity was demonstrated at all doses between 200 and 1800 mg/day. However, in chemotherapy-naïve patients, there was a trend to greater PSA suppression at the higher dose of 1400 mg/day when compared with 200 mg/day (HR 0.47, 95% CI 0.12 to 1.82, p=0.27). Treatment-related toxicities were observed in 27 patients (35%). The most frequent toxicities were fatigue/asthenia (10.4%), diarrhoea (5.2%), anorexia (5.2%) and hot flushes (3.9%), but most were graded as mild and no further dose reductions were made.

Retrospective analyses
Two studies investigated retrospectively the impact of starting enzalutamide at >50% dose on metastatic prostate cancer outcomes. Of 111 patients treated in the first study, 32 received a low dose (<80 mg/day) and 79 the standard dose (160 mg/day). Men who received low-dose enzalutamide had poorer Eastern Cooperative Oncology Group (ECOG) performance status and more comorbidities, although baseline PSA, doubling time and distribution of metastases were similar between the groups. The study found that men receiving low-dose enzalutamide had better longevity (restricted mean attained age: 89.1 years in low-dose enzalutamide vs 83.3 years in standard dose patients, p=0.025), as well as fewer adverse events. In a similar analysis of 59 patients with metastatic prostate cancer aged ≥75 years, 43 men received low-dose enzalutamide (≤80 mg/day) and 16 the standard dose (160 mg/day). PSA response (reduction of ≥50% from baseline) was observed in 18 (45%) and 10 (67%) patients receiving low and standard-dose enzalutamide at 12 weeks (p=0.15), respectively. No significant difference in OS or PSA PFS was observed between the two groups.

A retrospective, longitudinal cohort study of 6069 US veterans with metastatic CRPC explored the impact of relative dose intensity (RDI) of enzalutamide on PSA progression (defined as PSA ≥2 ng/mL and ≥25% above the nadir). In total, 924 (67.2%) men taking enzalutamide had at least one RDI <80% over at least 2 months, and this was associated with a higher risk of PSA progression (HR 1.26, 95% CI 1.09 to 1.46). No assessment of the impact of lower enzalutamide doses on PFS or OS was performed due to limited data.

A post-hoc analysis of 72 patients with MHSPC explored the effect of apalutamide dose reduction on skin-related adverse events and survival, comparing two groups receiving standard dose (240 mg/day) and reduced dose (60–180 mg/day) regimens. There was no significant difference in the incidence of skin-related adverse events between the two dose groups. There were no significant differences in progression to castrate resistance among those receiving the standard or a reduced dose of apalutamide, nor between patients with and without skin-related adverse events.

Post-hoc analysis of RCT
A post-hoc analysis of 1052 patients in the phase III randomised controlled TITAN trial examined the relationship between the pharmacokinetics of apalutamide exposure, efficacy and safety outcomes using a multivariate Cox regression model. Primary analysis of the trial found that apalutamide at a planned dose of 240 mg/day plus ADT improved survival versus placebo in patients with MHSPC, but some men received lower doses. No statistical association was detected between OS, PFS and apalutamide exposure quartiles. Incidence of skin rash and pruritus increased significantly with higher apalutamide exposure.

DISCUSSION
This review identified peer-reviewed evidence that reported on primary outcomes related to reduced-dose enzalutamide, apalutamide and darolutamide in men with metastatic prostate cancer. The findings suggest that each drug could be given at lower than the registered dose without potential loss of antitumour activity, and with a probable decrease in toxicity due to off-target effects.

There is an unmet need for assessing the potential benefits of lower-dose anticancer treatments, particularly in frail or comorbid patients who may experience substantial toxicity when given registered doses. The development of anticancer drugs continues to rely on historical paradigms for cytotoxic chemotherapy (maximum tolerated dose, MTD) which is rarely reconsidered after approval or labelling. Modern targeted therapies bind to specific molecules, and often there is no increase in efficacy beyond a certain dose, making the MTD concept irrelevant for new generation of anticancer agents. Phase I trials of enzalutamide, apalutamide and darolutamide do not show evidence of a relationship between increased drug exposure and efficacy near the labelled dose, suggesting that lower doses of these drugs may have near-equivalent efficacy in metastatic prostate cancer.

Cancer care is challenged by high drug expenditures and an ageing population, and it is important to identify safe, effective, less expensive dosing regimens. There is substantial financial toxicity associated with the 'utamides to patients (where medication costs are not covered) and to healthcare payers. Daily doses of enzalutamide, apalutamide and darolutamide are given with multiple pills, so reducing the dose may be a simple strategy, and if shown equally effective, may increase access to treatment and reduce financial toxicity. Dose reduction to improve tolerability or to counteract potential drug–drug interaction with existing medication may derive additional health economic benefit from cost-savings and improvement in quality of life from fewer, less severe toxic effects.

In this review, we have summarised preliminary evidence to suggest that lower doses of the 'utamides can maintain efficacy and reduce toxicity. There are also several meeting reports and individual case reports.
that show good or maintained oncological responses with low doses of enzalutamide. Other limited retrospective studies of anti-androgen drugs found that lower doses did not decrease the incidence of adverse events but did result in lower PSA response rates, although this did not impact on clinical disease progression or OS.20,40,41

Prostate cancer is common in older men, who are vulnerable to side-effects and drug interactions with existing medications. A few small studies have explored the feasibility of using reduced-dose enzalutamide, apalutamide or darolutamide in elderly patients and those with poor ECOG performance status,33,36,42 and report comparable survival outcomes and fewer treatment-related adverse events. However, sample numbers in these studies were small, the duration of follow-up limited and the studies were potentially subject to confounding by indication; the results need to be validated in a prospective study using prespecified reduced anti-androgen drug doses. Alternative approaches to de-escalation in the treatment of metastatic castration-sensitive prostate cancer to balance both the benefits and long-term risks and burden of treatment are under exploration.13,44

A limitation of this rapid review is that the results may be susceptible to selection bias, systematic error in the assessment and synthesis of results, or the omission of key studies.19 The search strategy was limited to English-language and full-text studies only, and it did not include a formal quality assessment of the risk of bias, due to the rapid nature of the review, the range of studies included and limited tools available for appraising phase I studies.

Standard dosing of enzalutamide, apalutamide and darolutamide may require reduction because of adverse events, but there are limited data on long-term clinical outcomes at lower doses. This review provides evidence that enzalutamide, apalutamide or darolutamide could be given at a lower than the standard recommended dose without likely loss of antitumour activity, and lower doses may lead to a decrease in toxicity. A prospective randomised trial comparing reduced and standard doses of enzalutamide, apalutamide and darolutamide is needed to investigate the efficacy of lower-dose regimens.

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Contributors AC and IFT proposed the rationale for conducting the study, AC, DCG, IFT and MV formulated the provisional study background and objectives. HLB wrote the initial review protocol. HLB and MV were responsible for the data searches, application of inclusion and exclusion criteria, and data collection. HLB analysed the data and drafted the initial manuscript. HLB, MV, DCG, PH, KR, IFT and AC were involved in the write-up, modification and revisions of the first manuscript. All authors are responsible for the revisions made to the final manuscript. HLB is the acting guarantor for the manuscript.

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Competing interests Ananya Choudhury is the Editor-in-Chief.

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

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. All data relevant to the study are included in the article or uploaded as supplemental information.

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REFERENCES


44 Janssen Research & Development. A study of an intermittent ADT approach with apalutamide monotherapy in participants with mCSPC. Available: https://clinicaltrials.gov/study/NCT05884398
Supplemental material (S1)

S1: Search strategy used in the rapid review

Database: Embase <1974 to 2023 June 18>, Ovid MEDLINE(R) ALL <1946 to June 18, 2023>

Search Strategy:

1. (prostat* adj3 (cancer* or tumo* or neoplas* or carcinom* or malign*)).tw.
2. Prostatic Neoplasms/ or prostate cancer/
3. (enzalutamide or apalutamide or darolutamide or Xtandi or Erleada or Nubeqa).mp.
4. Androgen Antagonists/ or Androgen Receptor Antagonists/ or enzalutamide/ or apalutamide/ or darolutamide/ or androgen receptor antagonist/ or antiandrogen/ (37758)
5. ((dose or doses or dosage* or medication) adj1 (change* or changing or reduce* or reduction or escalation or response)).tw. or "Dose-Response Relationship, Drug"/ or drug dose regimen/ or drug dose reduction/ or drug underdose/ or recommended drug dose/
6. 1 OR 2
7. 3 OR 4
8. 5 AND 6 AND 7
9. Remove duplicates from 8
### S2: Detailed summary of included studies (n=10)

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<tr>
<th>Study</th>
<th>Drug and Dose</th>
<th>Population</th>
<th>Methods and design</th>
<th>Adverse events</th>
<th>Key Outcomes</th>
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<tr>
<td>Akaza (Akaza et al., 2016) 2016 Phase I/II trial</td>
<td>Enzalutamide</td>
<td>Patients with metastatic castrate resistant prostate cancer, post doxetaxel ECOG 0-1</td>
<td>Multi-centre open-label uncontrolled phase I/II trial in Japan</td>
<td>AE related to drug:</td>
<td>During phase I, enzalutamide was well tolerated in each cohort; median duration of exposure in each group was 584.0, 171.0 and 252.0 days. Pharmacokinetics were dose-proportional after a single dose ranging from 80 to 240mg. Prostate-specific antigen response rate (≥50 % reduction from baseline) was 28.9% at 160mg/day at 12 weeks. Fewer serious treatment-emergent adverse events reported in phase I at lower doses (22.2% vs 34.2%).</td>
</tr>
<tr>
<td>Fizazi (Fizazi et al., 2014) 2014 Phase I/II trial</td>
<td>Darolutamide</td>
<td>Men with progressive metastatic castration-resistant prostate cancer (CRPC) ECOG 0-1</td>
<td>ARCADES trial: open label multi-centre Phase I (dose escalation)/ Phase II (dose expansion) trial in 23 hospitals across Europe and USA</td>
<td>In phase I, three patients reported eight adverse events of grade 3 and one patient had a grade 4 adverse event (lymphoedema), none of which were deemed to be related to treatment. Phase II: most common AE were</td>
<td>Primary endpoint safety and tolerability (Phase I) and proportion with a PSA response (50% or greater decrease in serum PSA) at week 12 in Phase II. In phase I, no dose-limiting toxic effects were reported and the maximum tolerated dose was not reached. In phase II, 38 patients who received 200 mg, 39 who received 400 mg, and 33 who received 1400 mg were assessable for PSA response at 12 weeks.</td>
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</tbody>
</table>
| Fizazi (Fizazi et al., 2017) 2017 | **Phase I/II trial (extended follow up)** | **Darolutamide 200-1800mg** | **Patients with castration-resistant prostate cancer (CRPC).**  
Extended follow-up in CYP17 inhibitor (CYP17i)-naive patients. | **Extended follow up in CYP17 inhibitor naïve patients from ARCADES trial.**  
Multicentre phase I/II trial of 134 patients, 77 of who were deemed CYP17 inhibitor naïve.  
Patients (n = 77) received oral ODM-201 twice daily at daily doses of 200-1800 mg | **The majority of AEs (61.1%) were mild (grade 1); the most common AE was fatigue/asthenia (35.1% of patients), with no clear relationship to darolutamide.**  
≥1 adverse event in 75/77 (97.4%) patients.  
Treatment related AEs occurred in 27 patients (35.1%)  
Commonest treatment related AE were fatigue (10.4%), diarrhoea (5.2%), anorexia (5.2%) and hot flushes (3.9%) | **Phase II: 11 (29%) patients in the 200 mg group, 13 (33%) in the 400 mg group, and 11 (33%) in the 1400 mg group achieved a PSA response at 12 weeks.** | **Median treatment duration 8.2 months (95% CI 5.6-11.0).**  
Median time to PSA progression was 25.2 months (95% CI 11.3-25.2) for chemotherapy-naive men and not reached (NR; 95% CI 5.5-NR) for chemotherapy-pretreated patients; a trend for improved antitumour response was observed for chemotherapy-naive patients.  
Median time to radiographic progression was longer for chemotherapy-naive (14.0 mo, 95% CI 8.1-33.3) than for chemotherapy-pretreated (7.2 mo, 95% CI 2.7-11.0) patients.  
For patients receiving expanded dose levels (n = 68; 200, 400 and 1400 mg/d), the HR for PSA progression was 0.47 (95% CI 0.12–1.82; p = 0.2743) for the 1400 mg/d group and 1.32 (95% CI 0.48–
<table>
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<tr>
<th>Study</th>
<th>Treatment</th>
<th>Study Population</th>
<th>Key Findings</th>
</tr>
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<tr>
<td>Freedland (Freedland et al., 2021) 2021 Retrospective cohort study</td>
<td>Enzalutamide Reduced dose enzalutamide (&lt;80%)</td>
<td>Patients with metastatic castration-resistant prostate cancer (mCRPC). Longitudinal cohort study of 6069 US Veteran health electronic data between 2010 and 2016. PSA progression defined as first rise in PSA &gt;2 ng/mL and 25% above nadir. Relative dose intensity (RDI) defined as ratio of total dispensed dose over the last two months to the standard recommended dose. Dose reduction assessed using a threshold of RDI &lt;80%. No data on adverse events was reported in the main analysis. Mean follow up 12.3 months. 67.2% enzalutamide patients had &gt;1 occurrence of RDI &lt;80%, with averaged dose reduction of enzalutamide at 59% standard 160mg/day dose. Multivariate Cox proportional hazards model suggested an RDI &lt;80% was associated with statistically significant higher risk of PSA progression HR [95% CI 1.258 [1.080–1.464], p&lt;0.003). No assessment of PFS or OS reported.</td>
<td></td>
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<tr>
<td>Oishi (Oishi et al., 2022) 2022 Retrospective analysis</td>
<td>Apalutamide 240mg or reduced dose (60-180mg/day) Multi-centre retrospective study of 107 patients (35nmCRPC and 72 mCRPC) treated with apalutamide between June 2019-2022. Classified into two groups: those treated with standard dose (240mg/day) n = 65 (67%), and those treated with reduced dose (60-180mg/day) n = 42 (39.3%). Median apalutamide dose in reduced group 180mg/day. Primary outcome was the effect of apalutamide dose reduction on skin related adverse events. Incidence of skin-related AEs in the full dose (55.4%; n = 36) and reduced dose (42.9%; n = 18) groups was not significantly different (p = 0.761). Treatment-related AEs other than skin related AEs were observed in 6 (5.6%) patients: fatigue, hepatic impairment, palpitation, interstitial</td>
<td>Overall skin-related AE rate was not significantly different between dose groups (55% vs. 43%, p=0.761). But incidence of skin-related AEs was significantly lower in patients with small body sizes (body weight &lt;67kg and body mass index &lt;24kg/m2) in the reduced dose apalutamide group (p 0.032). In the 72 patients with mCSPC, CRPC-free survival was not significantly different between the full and reduced dose apalutamide groups. Skin-related AE-free survival was not significantly different between standard</td>
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<tr>
<td>Study</td>
<td>Drug</td>
<td>Patients Characteristics</td>
<td>Findings</td>
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<tr>
<td>Rathkopf (Rathkopf et al., 2013) 2013</td>
<td>Apalutamide</td>
<td>Patients with progressive metastatic CRPC were assigned sequentially to escalating dose levels of apalutamide, between 30-480mg</td>
<td>Phase I study of 30 patients with progressive CRPC received continuous daily oral apalutamide at doses between 30 and 480mg.</td>
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<tr>
<td>Scher (Scher et al., 2010) 2010</td>
<td>Enzalutamide</td>
<td>Patients with progressive, metastatic castration-resistant prostate cancer</td>
<td>Phase I/II study undertaken in 140 patients in USA.</td>
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</table>

- Pneumonia, and renal dysfunction.
- Apalutamide discontinuation was significantly higher in patients receiving the standard dose, n = 18 (50%), than the reduced dose n = 3 (16.7%) group.
- Pharmacokinetics were linear and dose proportional.
- PSA decline at 12 weeks (≥50% reduction from baseline) observed in 46.7% patients.
- Reduction in FDHT uptake observed at all doses, with a plateau in response at ≥120-mg dose, consistent with saturation of AR binding.
- Dose escalation to 480 mg did not identify a maximum-tolerated dose.
- Primary objective was to identify the safety and tolerability of enzalutamide and to establish the maximum tolerated dose.
- Fatigue highest in doses ≥240mg/day
- Commonest overall AEs: fatigue, nausea, dyspnoea, anorexia and back pain.
- Two seizures occurred in patients receiving doses of 600mg and 360mg/day.
- PET imaging of 22 patients to assess androgen-receptor blockade showed decreased binding at doses from 60 mg to 480 mg per day (range 20–100%).
- Median time to progression was 47 weeks (95% CI 34–not reached) for radiological progression.
- Maximum tolerated dose for sustained treatment (>28 days) was 240mg.

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<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>Patients</th>
<th>Analysis</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>T’Jollyn (T’Jollyn et al., 2022) 2022</td>
<td>Apalutamide</td>
<td>Standard dose 240mg/day</td>
<td>Patients with metastatic castration-sensitive prostate cancer ECOG 0-1</td>
<td>Retrospective analysis of 1052 patients in phase III TITAN trial</td>
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<td>Compared with quartiles of dose exposure based</td>
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<td>1052 patients were randomised to Apalutamide + androgen-deprivation therapy (n=525) or Placebo + androgen-deprivation therapy (n=527). Cox regression analysis investigated the relationships between apalutamide exposure and overall survival and radiographic progression-free survival at apalutamide exposure quartiles.</td>
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<td>Incidence of skin rash and pruritis increased significantly with increasing apalutamide exposure.</td>
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<td>No statistical association was detected between overall survival and apalutamide exposure quartiles. No statistical association was detected between radiographic progression-free survival and apalutamide exposure quartiles, within a narrow apalutamide exposure range (coefficient of variation 22%).</td>
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<tbody>
<tr>
<td>Vinh-Hung (Vinh-Hung et al., 2022) 2022</td>
<td>Enzalutamide</td>
<td>Standard dose (160mg/day) vs low-dose (≤80mg/day)</td>
<td>Patients with metastatic prostate cancer</td>
<td>Retrospective review of 111 patients with metastatic prostate cancer treated with enzalutamide at a Caribbean single centre in 2014-2020.</td>
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<td>79 patients received standard dose (160mg/day) and 32 patients received low-dose (≤80mg/day) enzalutamide.</td>
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<td>Limited data reported in the analysis</td>
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<td>Patients taking low-dose enzalutamide reported less prior chemotherapy exposure, worse ECOG performance status, more comorbidities, including cardiovascular disease. OS and PFS did not differ between low-dose and standard dose groups.</td>
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</table>
• Primary outcome restricted mean survival time and restricted mean attained age using Irwin methods
• Secondary outcomes were OS, PFS, PSA progression.

Patients on low-dose enzalutamide had a better longevity with significantly longer RMAA, 89.1 years, versus standard-dose RMAA of 83.8 years (P = .003).
• In a subgroup analysis by age at start of enzalutamide, < 75 versus ≥75 years, longevity was also better with low-dose in younger patients (Δ = 2.9 years, P = .034, and older, Δ = 3.3 years, P = .011)

Vinh-Hung
(Vinh-Hung et al., 2020) 2020
Retrospective analysis

Enzalutamide
Standard dose (160mg/day) vs low-dose (≤80mg/day)

Patients aged ≥75 years with metastatic prostate cancer

• Retrospective review of 59 patients with metastatic prostate cancer treated with enzalutamide at a single centre in Caribbean between 2014-2020.
• Of 59 patients, 43 received standard dose (160mg/day) and 16 patients received low-dose (≤80mg/day) enzalutamide.
• Median follow up of 1 year.

• No adverse cardiovascular or neurological events were reported in the low dose group.
• Grade 4 fatigue reported in two patients in the standard dose group.

• PSA decrease of ≥50% at 12 weeks was observed in 67% patients (10/15), versus 45% with standard dose.
• Median progression-free survival was 11.2 months in low-dose group, versus 11.9 months for patients receiving the standard dose (P = 0.612).
Supplementary material 3: Further PK/PD data from phase I studies

In phase I/II studies, the pharmacokinetic profiles of enzalutamide were linear by dose range (Scher et al. 2010). Half-life was approximately 1 week and not affected by dose. Androgen-receptor binding was observed at all doses. Despite an almost linear increase in serum concentration with dose, no significant increase to target binding was observed from 60mg to 360mg per day on FDHT-PET scan. PSA decrease from baseline at 12 weeks were observed at all doses; the extent of decrease and proportion of patients recording a fall in PSA was dependent on the dose up to 150mg/day, but there was no clear additional benefit recorded for higher doses.

Pharmacokinetics (peak plasma concentrations and AUC) of apalutamide were reported as dose proportional in phase I/II studies (Rathkopf et al. 2013). Plasma concentrations declined slowly, with a mean half-life at steady-state of 3-4 days. Drug half-life and time to steady-state were independent of dose. Plasma trough concentrations increased steadily with time in proportion to dose, with most patients reaching steady-state exposure following 3 weeks continuous apalutamide. Reduction in FDHT-PET/CT uptake (used to measure pharmacodynamic response) was observed at all doses, with a plateau in response at 120mg/day, consistent with saturation of AR binding. At 12 weeks, 14 (47%) patients had >50% decline in PSA compared with baseline.

In phase I studies, exposure of darolutamide at steady state increased in a linear, dose-related pattern up to 1400mg/day with steady state plasma concentration reached after 1 week of continuous treatment (Fizazi et al. 2014). Anticancer activity was noted across all doses. A PSA response (≥50% decrease in PSA) was observed by week 12 at all doses, although responses were lower in patients previously treated with CYP17 inhibitors and in patients who had previously received other chemotherapy. Median time to PSA progression was not reached in phase I-II trials at 12 weeks at all dose levels. No clear differences in in radiological soft tissue and bone disease response were noted by darolutamide dose at 12 weeks; median time to radiological progression was not reached for patients who were naïve to any chemotherapy (including CYP17 inhibitor). No clear differences were observed in response to dose darolutamide and circulating tumour cell levels at 12 weeks. Compared with baseline, 41 (82%) patients maintained favourable circulating tumour cell counts (<5 cells per 7.5ml of blood), although no clear differentiation by dose was defined. Extended follow up of the sub-group of 77 patients with CYP17 inhibitor naïve prostate cancer reported anti-cancer activity at all doses (Fizazi et al. 2017). The median time to PSA progression was not reached for in the sub-group of chemotherapy naïve patients receiving 200mg and 1400 mg/day of darolutamide, and was reported as 25.2 months (95% CI 4.7–25.2, IQR 4.7-25.2) for patients receiving 400 mg/day.
Supplementary Material References


