Androgen deprivation therapy is the standard of care for patients with advanced hormone-sensitive prostate cancer. Despite an initial response, most patients progress to castration-resistant prostate cancer (CRPC). The realization that CRPC remains driven by androgen receptor (AR) signaling has formed the basis for a new generation of agents targeting the AR axis. Two of these agents, abiraterone acetate and enzalutamide, have been shown to prolong overall survival in patients with CRPC. Several other AR inhibitors are currently in development for the treatment of CRPC. The present article reviews ODM-201, a new-generation AR inhibitor with a unique molecular structure, in the treatment of CRPC. The design of an ongoing Phase III trial (ARAMIS) of ODM-201 in men with non-metastatic CRPC is also discussed, at a disease stage for which there is currently no approved treatment.

**KEYWORDS:** androgen receptor inhibitors • castration resistant • efficacy • metastatic • non-metastatic • ODM-201 • pharmacodynamics • pharmacokinetics • prostate cancer • tolerability
to significantly prolong overall survival in men with metastatic CRPC (mCRPC) in large randomized, Phase III trials [9–13]. In addition, several other treatments, that is, sipuleucel-T [14], cabazitaxel [15] and radium-223 dichloride [16], have been shown to improve overall survival in patients with mCRPC and have become available for the treatment of CRPC. Finally, denosumab was shown to be better than zoledronic acid to prevent bone metastases [17]. The management of CRPC continues to evolve rapidly as further large-scale randomized trials of these and new agents get underway [18–22].

Other potent novel AR inhibitors are currently being developed for the treatment of CRPC, such as ARN-509 [23,24] and ODM-201 (Orion Corporation Orion Pharma, Espoo, Finland), currently in late-phase development. The purpose of the present article is to review the pharmacodynamics, pharmacokinetics, clinical efficacy and safety profile of ODM-201 in the treatment of CRPC.

Introduction to ODM-201

Chemistry

ODM-201 is a synthetic compound comprising a mixture (1:1) of two pharmacologically active diastereomers (ORM-16497 and ORM-16555). ODM-201 and its pharmacologically active metabolite, ORM-15341, are structurally distinct from any known anti-androgen [25].

Pharmacodynamics

In vitro receptor binding studies show that ODM-201 and its major metabolite, ORM-15341, bind to wild-type AR and function as wild-type and mutant AR inhibitors [25]. In AR-overexpressing cells (VCaP/LNCap), ODM-201, ORM-15341, enzalutamide and ARN-509 inhibited AR function by blocking nuclear translocation of the receptor, when compared to vehicle [22]. ODM-201 and its metabolite also inhibited the AR mutants AR F876L, AR W741L and AR T877A, while enzalutamide and ARN-509 both inhibited AR T877A and had partial agonist activity against AR F876L [25].

OMD-201 has also demonstrated promising in vivo anti-tumor activity in a murine castration-resistant VCaP xenograft model in which ODM-201 potently inhibited tumor growth with better efficacy when compared to enzalutamide [25].

No clinical data are yet available regarding testosterone levels in men with an intact androgen feedback loop treated with ODM-201; however, preclinical data show that in mice with VCaP tumors, enzalutamide significantly increased serum testosterone levels after 3 weeks of treatment, whereas ODM-201 did not [25].

In vivo data suggest the penetrance of ODM-201 and ORM-15341 through the blood–brain barrier is negligible after oral administration in mice [25]. Animals were dosed orally for 7 days with ODM-201 (25, 50 or 100 mg/kg, twice daily) or enzalutamide (20 mg/kg daily). Following treatment completion, blood:plasma levels for ODM-201 and enzalutamide were 1.9–3.9% and 27%, respectively, whereas after one dose of ARN-509 (10 mg/kg), the brain:plasma ratio was 62% [25].

The ability of ARN-509 to effectively penetrate the blood–brain barrier has been previously reported [24].

Pharmacokinetics & metabolism

The Phase I/II ARADES trial included a pharmacokinetic analysis of ODM-201 [26]. Twenty-four men with mCRPC received 200, 400, 600, 1000, 1400 or 1800 mg/day of oral ODM-201 in two divided doses. Plasma concentrations of the two diastereomers of ODM-201 (ORM-16497 and ORM-16555) and its major metabolite ORM-15341 were quantified by liquid chromatography tandem mass spectrometry. ODM-201 concentrations were considered to be the sum of the concentrations of both ORM-16497 and ORM-16555 [26].

ODM-201 was rapidly absorbed with a median time to maximum plasma concentrations (Cmax) of 3.0–5.1 h for ODM-201 and 1.5–5.0 h for ORM-15341 on day 1 [26]. Steady-state plasma concentrations were reached after 1 week of continuous treatment; no further increases in plasma concentrations were evident between weeks 2 and 4 (FIGURE 1) [26]. At steady state, exposure to ODM-201 (i.e., Cmax and area under the curve) increased linearly in a dose-related fashion up to a dose of 1400 mg/day and reached a plateau thereafter (FIGURE 1) [26]. The mean half-lives of ODM-201 and ORM-15341 were 15.8 and 10.0 h, respectively, at steady state and were independent of dose [26].

Interaction with food was evident when ODM-201 was administered after a high-calorie, high-fat meal, compared to administration during fasting [27]. After a single dose of 600 mg of ODM-201, area under the curve and Cmax values were approximately two-times higher and Cmax was delayed by 2–3 h after a high-fat meal compared to administration during fasting, indicating delayed gastric emptying of ODM-201 [27]. In ongoing trials of ODM-201 (e.g., ARAMIS), it is required that the drug is taken with food.

In vitro data suggest that ODM-201 has a low potential for CYP-mediated drug–drug interactions [28]. In HepaRG cells treated with 10 μM of each test compound, ODM-201 and ORM-15341 showed no induction of CYP3A4, whereas both enzalutamide and ARN-509 demonstrated induction potential. Further, ODM-201 showed no inhibition of CYP isoenzymes (CYP1A2, CYP2A6, CYP2B6, CYP3A4, CYP2C8, CYP2D6, CYP2C19 and CYP2C9) in human liver microsomes at clinically relevant concentrations. There was no detectable inhibition of CYP2E1.

Metastatic CRPC

Clinical efficacy

Promising preclinical data prompted a Phase I/II clinical trial (ARADES) to evaluate ODM-201 in men with progressive mCRPC [26]. ARADES was an open-label, multicenter trial with a Phase I dose-escalation stage followed by a randomized Phase II extension trial. The primary objectives of ARADES were to assess the safety and tolerability of ODM-201 (Phase I) and prostate-specific antigen (PSA) response (Phase II), defined
as a \geq 50\% reduction in serum PSA from baseline. Secondary objectives were to evaluate the pharmacokinetics and anti-tumor activity of ODM-201 using other parameters, including soft tissue response, bone lesion stabilization, changes in circulating tumor cell (CTC) counts, and time to PSA and radiographic progression.

Men with progressive mCRPC despite ongoing ADT and castrate serum testosterone levels (i.e., \(<0.5\) ng/ml) were enrolled. Prior CYP17 inhibitor therapy and previous treatment with up to two chemotherapy regimens was permitted. Patients were not excluded on the basis of a history of or being at risk of seizures.

In the Phase I part of ARADES, anti-tumor activity was evident with all six doses of ODM-201 tested (i.e., 200, 400, 600, 1000, 1400 and 1800 mg/day). A PSA response, that is a \geq 50\% reduction in serum PSA, was observed in 17 (81\%) of the 21 patients who had PSA samples at baseline and at week 12.

In the Phase II part, three doses were selected for testing: 200 and 400 mg/day doses were identified as the lowest effective doses from Phase I and 1400 mg/day was the highest tolerable, pharmacokinetic linear dose of OMD-201. Twelve patients from Phase I entered the Phase II part of the trial. In addition to these patients, 112 men were randomized and

Figure 1. Pharmacokinetics of ODM-201 at a steady state. (A) Mean steady-state concentrations of ODM-201; (B) ODM-201 mean peak concentrations (C\textsubscript{max}) by dose; (C) ODM-201 mean area under the curve (AUC\textsubscript{t}) by dose. Values shown are means and whiskers depict the standard deviations [26].
110 were treated with 200 mg/day (n = 38), 400 mg/day (n = 37) or 1400 mg/day (n = 35) of ODM-201. Randomization was stratified according to previous treatment, that is, chemotherapy-naive and CYP17 inhibitor-naive, post-chemotherapy and CYP17 inhibitor-naive, post-chemotherapy and CYP17 inhibitor-naive, and post-CYP17 inhibitor.

A PSA response, defined as a ≥50% reduction in serum PSA from baseline at week 12, was observed in all three dose groups of ODM-201. Among patients who had received a CYP17 inhibitor, 20.3 weeks (95% CI: 16.9–26.1) for those who had received chemotherapy but not a CYP17 inhibitor, and 19.3 weeks (95% CI: 14.1–27.1) for those who had received a CYP17 inhibitor.

Further supportive efficacy data are available from the Phase I ARAFOR trial [30], in which men with chemotherapy-inhibitor-naive CRPC were treated with 1200 mg/day of ODM-201. A PSA response, defined as a ≥50% decrease in PSA levels from baseline at week 12, was observed in 25 of 30 (83%) patients. A combined analysis of all chemotherapy-naive and CYP17 inhibitor-naive patients from the ARADES and ARAFOR trials [31] reported a PSA response rate, defined as a ≥50% decrease in PSA levels from baseline, of 85% (33 of 39 patients) after 12 weeks. In most cases, there was a marked and durable decline in PSA levels in either soft tissue responses or bone stabilization, although patient numbers were small within each dose group.

CTC counts were assessed in 87 of 124 patients at week 12 [26]. Compared with baseline, 41 (82%) patients maintained favorable CTC counts (i.e., <5 cells/7.5 ml blood) at week 12. Among patients with unfavorable counts (≥5 cells/7.5 ml blood) at baseline, 14 (38%) converted to favorable counts and 9 (18%) patients changed from favorable to unfavorable counts. There were no clear differences between ODM-201 dose levels with regard to CTC changes.

The median time to PSA progression (≥25% increase in PSA from nadir according to Prostate Cancer Working Group-2 criteria) in Phase I/II patients was 72.3 weeks (95% CI: 24.3–not reached) for patients who were naïve to both chemotherapy and CYP17 inhibitors, 20.3 weeks (95% CI: 16.9–26.1) for those who had received chemotherapy but not a CYP17 inhibitor, and 19.3 weeks (95% CI: 14.1–27.1) for those who had received a CYP17 inhibitor.

Safety & tolerability

Safety data from the ARADES [26] and ARAFOR [30] trials show that ODM-201 is well tolerated. The ARADES trial included the largest patient cohort treated to date with ODM-201; a summary of the most common adverse events by grade reported in the ARADES safety population is shown in Table 2. The most common adverse events (all grades) were fatigue or asthenia (31%), back pain (21%), arthralgia (16%) and pain (15%). Most adverse events (91%) were mild or moderate in severity (grade 1 or 2). Grade 3 and 4 adverse events were reported in 27 (22%) and 2 (<2%) patients, respectively. ODM-201 was tolerated up to the highest dose of 1800 mg/day, and the maximum tolerated dose was not
reached. None of the adverse events appeared to be dose related. No seizures were noted during the trial.

Most events were deemed by the investigators to be related to prostate cancer rather than ODM-201 [26]. Adverse events which were considered to be drug related occurred in 44 (35%) patients, and included fatigue or asthenia in 15 (12%), hot flushes in 6 (5%), decreased appetite in 5 (4%), diarrhea in 3 (2%) and headache in 3 (2%). One grade 3 event (fatigue or asthenia) and no grade 4 adverse events were judged to be related to ODM-201.

A retrospective analysis of the ARADES safety database was performed specifically to identify seizure-related or CNS-related adverse events [32]. A total of 16 patients reported at least one CNS-related adverse event during the trial, that is, fall episodes (n = 6), urinary incontinence (n = 5), collapse (n = 2), fecal incontinence (n = 2), syncope (n = 1) and pre-syncope (n = 1). All events, except one case of urinary incontinence, were considered by the investigator as unrelated to ODM-201. None of the events were considered to be seizure like and none of them led to trial discontinuation. One seizure event was reported in a patient 27 days after stopping ODM-201. Anemia was a confounding factor in this patient and the patient had previously reported having collapses. Patients in the ARADES trial received 38 medications for indications to treat epilepsy or other seizure-related disorders (i.e., insomnia, n = 11; anxiety, n = 8; pain, n = 10; epilepsy, n = 3; depression, n = 2; polyneuropathy, alcohol abuse, bowel incontinence, restless leg syndrome; n = 1 case each).

Non-metastatic CRPC
Non-metastatic CRPC is a distinct disease state which is characterized by rising PSA levels despite castrate levels of testosterone, and without radiological evidence of metastatic disease. It is a major challenge for clinicians as no treatments are currently approved for this stage of the disease. Current treatment guidelines recommend participation in a clinical trial, observation, or second-line endocrine therapy with first-generation anti-androgens, ketoconazole, diethylstilbestrol or other estrogens [2], although the data supporting the use of these agents remain limited [33].

Non-metastatic CRPC presents an opportunity to intervene with therapy designed to delay progression to metastatic disease and is an active area of research. Several randomized trials have investigated bone-targeted agents in non-metastatic CRPC to prevent bone metastases, but most have reported negative results [34–36]. Although an improvement in overall survival was not observed, denosumab was able to delay the onset of metastatic disease [37]. As there is a strong rationale for the further application of hormonal manipulation in patients with CRPC, a Phase III trial of ODM-201 has recently been initiated in this setting, ARAMIS; clinical trials.gov identifier [38]. A schematic diagram of the design of the ARAMIS trial is shown in Figure 3.

ARAMIS is a multinational, randomized, double-blind, placebo-controlled trial designed to test the superiority of ODM-201 600 mg twice daily compared with placebo in men with high-risk non-metastatic CRPC, that is, those with a PSA doubling time of ≤10 months. Patients with metastatic or symptomatic locoregional disease are excluded. Prior use of the following treatments is not permitted: second-generation AR inhibitors, such as enzalutamide and ARN-509; CYP17 enzyme inhibitors, such as abiraterone acetate, TAK-700 or ketoconazole; chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment

| Table 2. ARADES study: adverse events occurring with 200–1800 mg/day of ODM-201 in >10% of patients (safety population, n = 134) [36]. |
|-----------------|----------------|----------------|----------------|----------------|
| Adverse event   | Grade 1 (%)    | Grade 2 (%)    | Grade 3 (%)    | Total (%)      |
| Fatigue or asthenia | 30 (22%)   | 13 (10%)       | 2 (1%)         | 41 (31%)       |
| Back pain       | 17 (13%)      | 13 (10%)       | 2 (1%)         | 28 (21%)       |
| Arthralgia      | 18 (13%)      | 9 (7%)         | 2 (1%)         | 22 (16%)       |
| Pain            | 9 (7%)        | 8 (6%)         | 3 (2%)         | 20 (15%)       |
| Constipation    | 15 (11%)      | 5 (4%)         | 0              | 18 (13%)       |
| Nausea          | 14 (10%)      | 4 (3%)         | 0              | 17 (13%)       |
| Decreased appetite | 15 (11%)   | 1 (<1%)        | 0              | 16 (12%)       |
| Peripheral edema | 14 (10%)   | 2 (1%)         | 0              | 16 (12%)       |

*Total may be less than the sum of the grade because patients may have had adverse events of several grades.
completed more than 2 years before randomization; radiation therapy or osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomization; estrogens, 5α-reductase, AR inhibitors or systemic corticosteroids within 28 days before randomization. Patients receiving osteoclast-targeted therapy to prevent osteoporosis-related bone loss may continue treatment at the same dose and schedule.

The trial was initiated in August 2014. It has an enrollment target of 1500 patients, who will be treated until confirmed metastasis or death for a total duration of up to 72 months (6 years). The primary trial endpoint is metastasis-free survival, defined as time from randomization until evidence of metastasis or death from any cause, whichever occurs first. Upon central confirmation of metastasis, a patient will be withdrawn from trial treatment and then followed every 16 weeks for secondary and additional trial variables.

The double-blind part of the trial will continue until the predefined number of metastatic events has been reached (approximately 572 events). At this time, patients in the ODM-201 group will continue trial treatment, and patients in the placebo arm must discontinue trial treatment and will not be allowed to crossover to ODM-201. Patients from the placebo group will then be treated with standard of care at the discretion of the investigator and followed every 16 weeks for secondary and additional variables.

Conclusions
ODM-201 is a next-generation AR inhibitor which has strong affinity for the AR receptor and has demonstrated anti-tumor activity in a murine CRPC xenograft model. ODM-201 also suppressed AR mutants known to confer resistance to second-generation anti-androgens. In contrast to other second-generation AR inhibitors, preclinical studies indicate that the brain penetration of ODM-201 is negligible, suggesting this agent may be associated with a lower risk of seizures. Findings from a large multicenter Phase I/II clinical trial in men with mCRPC show that ODM-201 has promising anti-tumor
activity in both chemotherapy-naïve and chemotherapy-pretreated patients. ODM-201 has a favorable tolerability profile and no seizures have been reported with this agent. A placebo-controlled, randomized Phase III trial of ODM-201 in men with non-metastatic CRPC has recently been initiated.

Expert commentary
ODM-201 is a novel AR inhibitor that is structurally distinct from all known anti-androgens. Preclinical data indicate that ODM-201 and its major metabolite bind to AR with high affinity, and ODM-201 achieves a significantly better inhibition of tumor growth compared to enzalutamide in a murine castration-resistant VCaP xenograft model [25]. ODM-201 also shows inhibitory activity, without evidence of agonism, against several mutant ARs implicated in resistance to other second-generation AR inhibitors [25]. These include AR F876L, which causes antagonist-to-agonist switching with both enzalutamide and ARN-509 in preclinical models of prostate cancer [23,39] and which has been identified in plasma DNA from patients with progressive CRPC treated with ARN-509 [23,25]. Inhibition of the AR pathway is demonstrated to be an effective treatment strategy for men with progressive mCRPC. Enzalutamide and abiraterone acetate initially showed promising efficacy data in Phase I/II trials, including ≥50% reduction of serum PSA and soft tissue and bone responses in all patient groups (i.e., chemotherapy naïve and chemotherapy pretreated) [40,41]. The initial efficacy shown by these agents, now licensed for use, was confirmed by subsequent Phase III trials that reported significantly improved survival in men with mCRPC [10,42]. ARN-509, a new second-generation AR inhibitor, has shown favorable efficacy in a Phase I trial [43] with the Phase II trials ongoing.

The promising pharmacodynamic profile of ODM-201 prompted a large Phase I/II clinical trial in men with mCRPC [26]. ODM-201 showed encouraging anti-tumor efficacy, that is, ≥50% reduction of serum PSA, at all doses tested. Secondary endpoints, which included soft tissue responses, lack of bone progression, and time to PSA progression, were all supportive of the primary efficacy data. Patients who had not previously received chemotherapy and/or CYP17 inhibitors showed the best responses to ODM-201, an observation which has also been made with both enzalutamide [41] and abiraterone acetate [40].

ODM-201 has a favorable tolerability profile, and many of the adverse events reported with ODM-201 were considered to be disease-related rather than drug-related. Cross-trial comparisons of ODM-201 with enzalutamide and ARN-509 in patients with mCRPC suggest that there may be differences in the rates at which some adverse events occur [11,12,26,43], but direct head-to-head comparisons are needed to confirm these trends.

The risk of drug-associated seizures is likely to be determined by drug concentrations achieved in the brain after oral administration [44], and AR inhibitors differ markedly with respect to their brain:plasma ratios. Both ODM-201 and its metabolite ORM-15341 have a low brain:plasma ratio in vivo and no seizures have been reported to date, even though patients with a medical history of seizures or patients at risk of seizures were eligible for all ODM-201 trials. In contrast, both enzalutamide and ARN-509 are known to cross the blood–brain barrier, and patients at risk of seizures have been excluded from clinical trials of both these agents. Despite the exclusion of at-risk patients, enzalutamide has been associated with several reports of seizures [11,12,41]. To date, no seizures have been reported with ARN-509 in humans, although only limited clinical data are available on this agent [43]. Safety data from the Phase III ARAMIS trial are required to confirm this aspect of the tolerability profile of ODM-201.

Non-metastatic CRPC offers a potential therapeutic window to decrease morbidity by delaying or preventing the development of distant metastases. The recent positive data for AR axis-targeted drugs in mCRPC and the recognized role of the AR in CRPC have provided a rationale for exploring AR inhibitors in non-metastatic CRPC. A Phase II trial of orteronel (TAK-700), an androgen synthesis inhibitor, in patients with non-metastatic CRPC reported durable reductions in PSA levels [45], though orteronel may not be further developed due to two recently reported negative Phase III trials for overall survival in mCRPC [46,47]. Three large randomized, placebo-controlled Phase III trials (ARAMIS, PROSPER and SPARTAN) have been initiated to investigate AR inhibitors in men with high-risk non-metastatic CRPC (Table 3) [38,48,49]. Data from these trials, the first of which is to be reported in 2015,

**Table 3. Ongoing international Phase III randomized trials with androgen receptor inhibitors in men with high-risk (i.e., prostate-specific antigen doubling time ≤10 months) non-metastatic castration-resistant prostate cancer.**

| Trial [identifier] | Estimated enrollment | Treatments | Primary endpoint | Ref. |
|--------------------|---------------------|------------|-----------------|------|
| ARAMIS [NCT02200614] | 1500 | ODM-201 600 mg twice daily, placebo | Metastasis-free survival | [38] |
| PROSPER [NCT02003924] | 1560 | Enzalutamide 160 mg once daily, placebo | Metastasis-free survival | [48] |
| SPARTAN [NCT01946204] | 1200 | ARN-509 240 mg once daily, placebo | Metastasis-free survival | [49] |
will help to define if there is a role for AR inhibitors earlier in the course of CRPC. A point of difference between the patient populations of these trials is that patients with a history of seizures or any predisposing conditions for seizures will be included in the ARAMIS study, but excluded from the other two trials.

**Five-year view**

It is likely that the future treatment of CRPC will continue to evolve rapidly as other major clinical trials reach their completion dates. A series of ongoing Phase III trials is currently investigating the addition of various treatments (i.e., abiraterone, zoledronic acid, docetaxel, enzalutamide plus abiraterone and/or radiotherapy) to ADT compared with ADT alone in men with newly diagnosed, hormone-sensitive metastatic prostate cancer. The first two of these trials, GETUG 15 and CHAARTED (E3805), reported a progression-free survival benefit with dual therapy, though overall survival was improved only in CHAARTED [56,57].

Several treatments have been shown to prolong overall survival in patients with mCRPC over the last 5 years, including abiraterone acetate, enzalutamide, sipuleucel-T, cabazitaxel and radium-223 dichloride, but none of these agents have been directly compared. Understanding how best to choose and combine treatments for CRPC is a key question which needs to be formally addressed. Retrospective data indicate that there may be cross-resistance between abiraterone acetate and enzalutamide [55,57] and abiraterone and docetaxel [51,54], although the latter scenario is unclear [55,56]. The activity of cabazitaxel is retained if given after abiraterone acetate [57]. Several prospective Phase II and III trials are currently in progress to examine questions regarding treatment sequencing (e.g., abiraterone and enzalutamide [58]; treatment sequencing in a prospective observational study [59]) and treatment combinations (i.e., enzalutamide plus abiraterone vs enzalutamide [60]; radium-223 dichloride plus abiraterone vs abiraterone [61]; radium-223 dichloride plus enzalutamide vs enzalutamide [62]; abiraterone plus luteinizing hormone-releasing hormone [63,64]) in patients with CRPC, and will help to guide decision-making in the future.

Clinical trials with appropriate endpoints will also be critical for addressing many of the questions that lie ahead in prostate cancer. Prostate cancer shows great heterogeneity, yet it is still treated as a single disease. This is in contrast to many other common cancers which are now subclassified and treated on the basis of molecular markers (e.g., KRAS in colorectal cancer, HER2 in breast and gastric cancers, and epidermal growth factor mutations and ALK gene fusions in non-small cell lung cancer). Predictive biomarkers are needed to identify patients most likely to respond to a particular treatment based on disease characteristics. Molecular biomarkers have been investigated in trials of abiraterone acetate in CRPC, that is, ERG rearrangements or serum androgens, but neither has been shown to be predictive of treatment benefit [65,66]. Future clinical trials should include correlative testing of molecular and other markers, so that predictive biomarkers for emerging agents can be identified. In addition, there are currently no reliable surrogate measures for overall survival in prostate cancer [1]. As the number of available treatment options increases, surrogate endpoints are needed to shorten the time required to complete a clinical trial and to allow a greater number of therapies to be tested at any given time. Promising surrogate endpoints for overall survival in prostate cancer include radiographic progression as defined by Prostate Cancer Working Group-2 [67], CTC enumeration [68] and AR splice variant 7 (AR-V7) in CTC [6], although no biomarker has yet met the regulatory analytical and clinical validation requirements for routine use.

It is likely that the management of patients with prostate cancer will change dramatically in the next few years. Multiple effective agents are now available to treat patients with metastatic and non-metastatic prostate cancer, yet large gaps in our understanding of how to use and sequence these agents remain [69]. A more comprehensive understanding of the molecular biology of prostate cancer will allow the identification of new therapeutic targets and the selection of therapy at an individual patient level.

**Financial & competing interests disclosure**

K Fizazi has participated in advisory boards for Orion Pharma. Writing and editorial assistance was provided by Harriet Lamb of Bioscript Medical, which was funded by Orion Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**Key issues**

- ODM-201 is a next-generation androgen receptor (AR) inhibitor with strong affinity for the AR receptor.
- ODM-201 suppresses AR mutants known to confer resistance to second-generation anti-androgens.
- Brain penetration of ODM-201 is found to be negligible in preclinical studies.
- ODM-201 has promising anti-tumor activity in chemotherapy-naïve and chemotherapy-pretreated men with metastatic castration-resistant prostate cancer.
- ODM-201 has a favorable tolerability profile, with no seizures reported to date.
- A placebo-controlled, randomized Phase III trial of ODM-201 in men with non-metastatic castration-resistant prostate cancer is underway.

ODM-201 has promising anti-tumor activity in chemotherapy-naive and chemotherapy-pretreated men with metastatic castration-resistant prostate cancer.
References

1. Massard C, Fizazi K. Targeting continued androgen receptor signalling in prostate cancer. Clin Cancer Res 2011;17:3876-83.
2. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 2, 2014. Available from: www.nccn.org/professionals/physician_gls/f_guidelines.asp
3. Horwich A, Hugosson J, de Reijke T, et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Ann Oncol 2013;24:1141-62.
4. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res 2008;68:4447-54.
5. Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res 2006;66:2815-25.
6. Antonarakis ES, Nakazawa M, Luo J. Resistance to androgen-pathway drugs in prostate cancer. N Engl J Med 2014;371:1028-38.
7. Shafi AA, Yen AE, Weigel NL. Androgen receptors in hormone-dependent and castration-resistant prostate cancer. Pharmacol Ther 2013;140:223-38.
8. Mostaghel EA, Marck BT, Plymate SR, et al. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res 2011;17:5913-25.
9. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152-60.
10. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.
11. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-54.
12. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213-23.
13. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zolendronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813-22.
14. Amsden. Open-label access protocol of denosumab for subjects with advanced cancer. Available from: http://clinicaltrials.gov/show/NCT01419717
15. Northwestern University. Zolendronate for the prevention of bone loss in men with prostate CA on long-term androgen deprivation. Available from: http://clinicaltrials.gov/show/NCT00058188.
16. Janssen Research & Development. Study of abiraterone acetate in patients with advanced prostate cancer. Available from: http://clinicaltrials.gov/show/NCT01217697.
17. Spanish Oncology Genito-Urinary Group. Study of weekly cabazitaxel for advanced prostate cancer. Available from: http://clinicaltrials.gov/show/NCT01518283.
18. Bayer. Radium(223) dichloride (alpharadin) in castration-resistant (hormone-refractory) prostate cancer patients with bone metastases. Available from: http://clinicaltrials.gov/show/NCT01618370.
19. Joseph JD, Lu N, Qian J, et al. A clinically relevant androgen receptor mutation confers resistance to second-generation antimandrogens enzalutamide and ARN-509. Cancer Discov 2013;3:1020-9.
20. Clegg NJ, Wongvipat J, Joseph JD, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. Cancer Res 2012;72:1494-503.
21. Moilanen A, Riikonen R, Oksala R, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signalling-directed prostate cancer therapies. Sci Rep 2015;5:12007.
22. Fizazi K, Massard C, Bono P, et al. ARADES study group. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. Lancet Oncol 2014;15:975-85.
23. Massard C, Tammela TLJ, Vjaters E, et al. A study of two ODM-201 formulations with a safety and tolerability extension phase in patients with metastatic chemotherapy-naive castration-resistant prostate cancer (CRPC). J Clin Oncol 2014;32(Suppl 4):abstr 115. Available from: www.orion.fi/globalassets/documents/ld/congress-posters/asco-gu-poster-massard-et-al-2014.pdf?id=9558&epslanguage=en.
24. Moilanen A, Riikonen R, Oksala R, et al. ODM-201 - new generation antiandrogen with excellent antiandrogenic and antitumor activity in nonclinical models of CRPC. Eur J Cancer 2013;49(Suppl 2):abstr 2869.
25. Scher HI, Halabi S, Tannock I, 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.
26. Massard C, Penttinen H, Bono P, et al. Pharmacokinetics, activity, and safety of ODM-201 in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: An open-label phase I trial with long-term extension. J Clin Oncol 2015;33(Suppl 7):abstr 230.
27. Tammela L, Massard C, Bono P, et al. European Urology Supplements. Safety and efficacy of ODM-201 in chemotherapy and CYP17-inhibitor naïve patients: Analysis of data from the ARADES and the ARAFOR trials (abstract 862). Presented at the 29th Annual European Association of Urology Congress, Stockholm, Sweden, 2014. Available from: www.urotoday.com/Prostate-Cancer/eau-2014-poster-safety-and-efficacy-of-odm-201-in-chemistry-and-cyp17-inhibitor-naive-patients-analysis-data-from-the-arades-and-the-arafor-trials.html.
28. Hong S, Lee HS, Park YS, et al. Discovery of ODM-201, a novel antiandrogen with enhanced antiandrogenic and antitumor activity in nonclinical models of CRPC. Eur J Cancer 2013;49(Suppl 2):abstr 2869.
29. Scher HI, Halabi S, Tannock I, 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.
30. Massard C, Penttinen H, Bono P, et al. Pharmacokinetics, activity, and safety of ODM-201 in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: An open-label phase I trial with long-term extension. J Clin Oncol 2015;33(Suppl 7):abstr 230.
31. Tammela L, Massard C, Bono P, et al. European Urology Supplements. Safety and efficacy of ODM-201 in chemotherapy and CYP17-inhibitor naïve patients: Analysis of data from the ARADES and the ARAFOR trials (abstract 862). Presented at the 29th Annual European Association of Urology Congress, Stockholm, Sweden, 2014. Available from: www.urotoday.com/Prostate-Cancer/eau-2014-poster-safety-and-efficacy-of-odm-201-in-chemistry-and-cyp17-inhibitor-naive-patients-analysis-data-from-the-arades-and-the-arafor-trials.html.
A clinical perspective. J Clin Oncol 2014; 32(Suppl 4):abst 275. Available from: http://meetinglibrary.asco.org/content/90517/media=vm

33. Tombal B. Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Ann Oncol 2012;23(Suppl 10):x251-8

34. Nelson JB, Love W, Chin JL, et al. Phase 3, randomized, controlled trial of atrasentan in patients with 13nonmetastatic, hormone-refractory prostate cancer. Cancer 2008;113:2478-87

35. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918-25

36. See comment in PubMed Commons below. Miller K, Moul JW, Gleave M, et al. Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2013;16:187-92

37. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800-6

38. Anon. Efficacy and safety study of ODM-201 in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS). Available from: http://clinicaltrials.gov/ct2/show/NCT02200614

39. Korpal M, Korn JM, Gao X, et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enazalutamide). Cancer Discov 2013;3:1040-6

40. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 2010;28:1496-501

41. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010;375:1437-46

42. Saad F, de Bono J, Shore N, et al. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial. Eur Urol 2015;67:223-30

43. Rathkopf DE, Morris MJ, et al. Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. J Clin Oncol 2013;31:3525-30

44. Foster W, Car BD, Shi H, et al. Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. Prostate 2011;71:480-8

45. Hussain M, Corn PG, Michaelson MD, et al. Prostate Cancer Clinical Trials Consortium, a program of the Department of Defense Prostate Cancer Research Program and the Prostate Cancer Foundation. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. Clin Cancer Res 2014;20:4218-27

46. Saad F, Fizazi K, Jinga V, et al. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. Lancet Oncol 2015;16:338-48

47. Fizazi K, Jones R, Oudard S, et al. Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. J Clin Oncol 2015;33:7273-31

48. Anon. Safety and efficacy study of enzalutamide in patients with non-metastatic castration-resistant prostate cancer (PROSPER). Available from: http://clinicaltrials.gov/ct2/show/NCT02003924

49. Anon. A study of ARN-509 in men with non-metastatic castration-resistant prostate cancer (SPARTAN). Available from: http://clinicaltrials.gov/ct2/show/NCT01946204

50. Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPRCa): An ECOG-led phase III randomized trial. J Clin Oncol 2014;32:5s; Suppl; abst LBA2

51. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149-58

52. Loriot Y, Bianchini D, Ilenea R, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807-12

53. Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol 2012;23:2943-7

54. de Bono JS, Smith MR, Saad F, et al. Response to taxane chemotherapy as first subsequent therapy after abiraterone acetate (AA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Post-hoc analysis of COU-AA-302. J Clin Oncol 2015;33(Suppl 7):abstr 184

55. Noonan KI, North S, Bitting RL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802-7

56. Schweizer MT, Zhou XC, Wang H, et al. The influence of prior abiraterone treatment on the clinical activity of docetaxel in men with metastatic castration-resistant prostate cancer. Eur Urol 2016:66:646-52

57. Al Nakouzi N, Le Moulec S, Albige L, et al. Cabazitaxel remains active in patients progressing after docetaxel followed by novel androgen receptor pathway targeted therapies. Eur Urol 2014;68(2):228-35

58. Anon. Sequencing abiraterone and enzalutamide in mCRPC. Available from: http://clinicaltrials.gov/ct2/show/NCT02125357

59. Anon. A registry to observe the treatment of prostate cancer under routine medical care. Available from: http://clinicaltrials.gov/ct2/show/NCT02236637

60. Anon. Enzalutamide with or without abiraterone acetate and prednisone in treating patients with castration-resistant metastatic prostate cancer. Available from: http://clinicaltrials.gov/ct2/show/NCT01949337

61. Anon. Radium-223 dichloride and abiraterone acetate compared to placebo and abiraterone acetate for men with cancer of the prostate when medical or surgical castration does not work and when the cancer has spread to the bone, has not been treated with chemotherapy and is causing no or only mild symptoms (ERA 223). Available from: http://clinicaltrials.gov/ct2/show/NCT02194842
63. Anon. Abiraterone acetate with or without LHRH-therapy in men with progressive chemotherapy-naïve CRPC. Available from: https://clinicaltrials.gov/ct2/show/NCT02077634

64. Fizazi K, Abrahamsson PA, Ahlgren G, et al. Achievements and perspectives in prostate cancer phase 3 trials from genitourinary research groups in Europe: introducing the prostate cancer consortium in Europe. Eur Urol 2014;67:904-12

65. Ryan CJ, Molina A, Li J, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol 2013;31:2791-8

66. Attard G, de Bono JS, Logothetis CJ, et al. Improvements in radiographic progression-free survival stratified by ERG gene status in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. Clin Cancer Res 2015;21:1621-7

67. Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol 2015;33:1356

68. Danila DC, Fleisher M, Scher HI. Circulating tumor cells as biomarkers in prostate cancer. Clin Cancer Res 2011;17:3903-12

69. Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: Recommendations of the St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC). Ann Oncol 2015;In Press