

EXPERT  
REVIEWS

# ODM-201: a new-generation androgen receptor inhibitor in castration-resistant prostate cancer

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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

Androgens and androgen receptor (AR) signaling pathways are the main oncogenic drivers of prostate cancer and the primary target for treatment [1]. Androgen deprivation therapy (ADT), either through bilateral orchiectomy or luteinizing hormone-releasing hormone agonists or antagonists, is the current standard of care for patients with advanced androgen-sensitive prostate cancer [2,3]. However, despite an initial response to ADT, patients invariably progress to castration-resistant prostate cancer (CRPC), even though their serum testosterone levels remain low [2].

It was believed for many decades that patients who progressed on ADT were ‘hormone refractory’, and that further hormonal manipulation would be ineffective. Treatment options at that time were limited to chemotherapy (e.g., docetaxel) or older second-line hormonal agents (e.g., diethylstilbestrol, ketoconazole), which have limited data supporting their efficacy.

However, our understanding of the hormonal drivers of CRPC has evolved considerably since then, prompting renewed interest in agents that target the AR axis. It is now recognized that up-regulation of intratumoral androgen biosynthesis enzymes occurs, leading to an increase in androgen levels despite ADT [4,5]. Other alterations include increases in AR expression due to gene amplification and overexpression, AR point mutations or splice variants that alter AR activity [6], changes in cell signaling pathways that modulate AR function and changes in co-regulator proteins [7].

Two agents targeting the AR axis have been recently approved for use in CRPC, namely abiraterone acetate, an irreversible CYP450-17 (CYP17)-inhibitor which inhibits extragonadal and intratumoral synthesis of androgens [8], and enzalutamide, a second-generation AR inhibitor. As proof of concept, both abiraterone acetate and enzalutamide have been shown

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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].

ODM-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 ( $C_{max}$ ) 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.,  $C_{max}$  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].

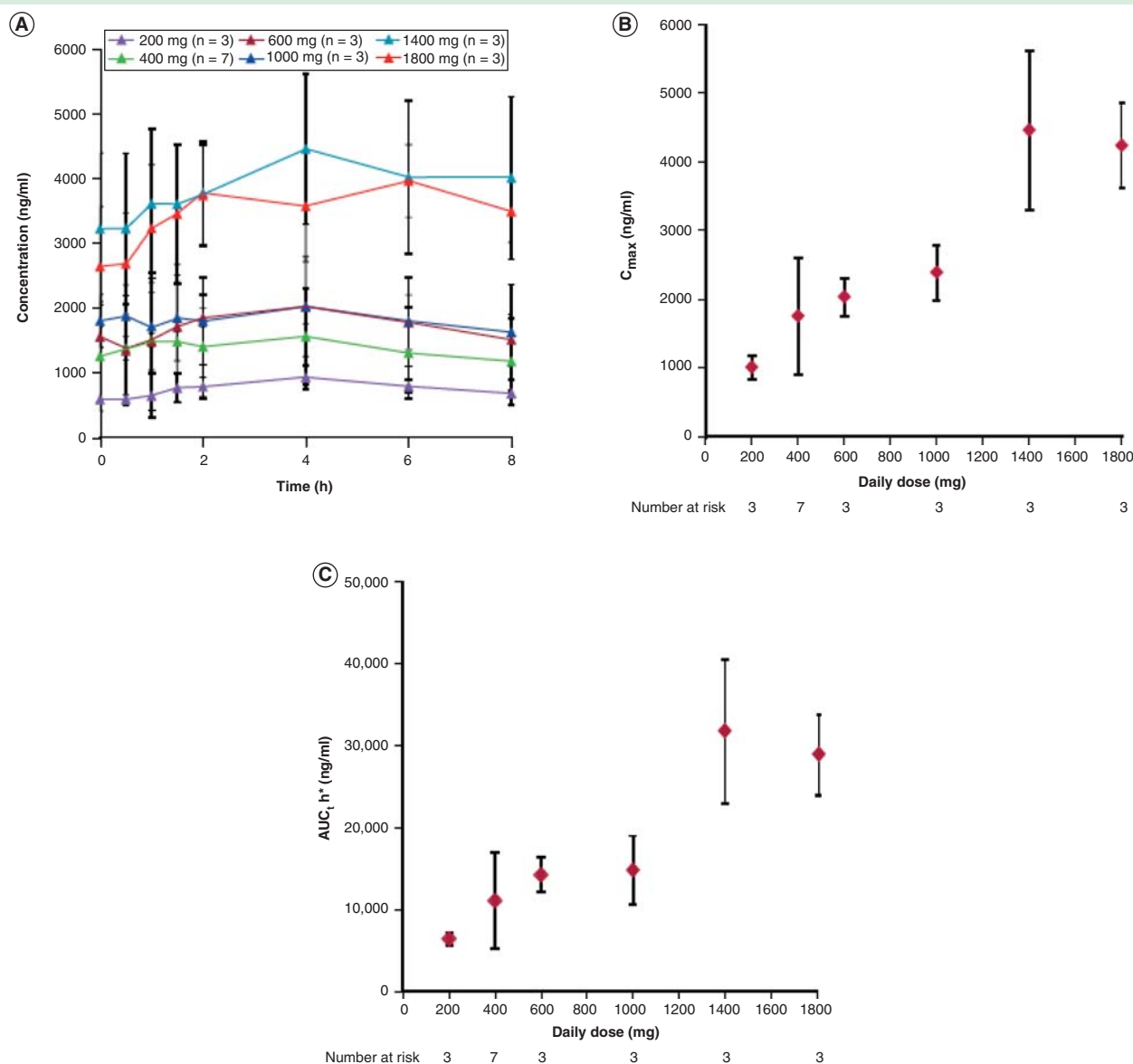
Interaction with food was evident when ODM-201 was administered after a high-calorie, high-fat meal, compared to administration during fasting [27]. After a single dose of 600 mg of ODM-201, area under the curve and  $C_{max}$  values were approximately two-times higher and  $C_{max}$  was delayed by 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  $\mu$ M 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



**Figure 1. Pharmacokinetics of ODM-201 at a steady state.** (A) Mean steady-state concentrations of ODM-201; (B) ODM-201 mean peak concentrations ( $C_{max}$ ) by dose; (C) ODM-201 mean area under the curve ( $AUC_0-8h$ ) by dose. Values shown are means and whiskers depict the standard deviations [26].

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

**Table 1. ARADES study: efficacy outcomes at 12 weeks** [26].

	ODM-201 dose (mg/day)		
	200	400	1400
<b>Primary outcome</b>			
≥50% decrease in serum PSA from baseline			
All evaluable patients	11/38 (29%)	13/39 (33%)	11/33 (33%)
Chemotherapy-naïve and CYP17i-naïve	6/12 (50%)	9/13 (69%)	6/7 (86%)
Post-chemotherapy and CYP17i-naïve	5/11 (45%)	1/9 (11%)	4/11 (36%)
Post-CYP17i	0/15	3/17 (18%)	1/15 (7%)
<b>Secondary outcomes</b>			
Objective response <sup>†</sup> (soft tissue)			
All evaluable patients	2/30 (7%)	6/28 (21%)	2/16 (13%)
Chemotherapy-naïve and CYP17i-naïve	1/9 (11%)	4/9 (44%)	1/2 (50%)
Post-chemotherapy and CYP17i-naïve	1/8 (13%)	0/7	1/5 (20%)
Post-CYP17i	0/13	2/12 (17%)	0/9
Stable disease (bone scan) <sup>‡</sup>			
All evaluable patients	20/31 (65%)	20/32 (63%)	19/28 (68%)
Chemotherapy-naïve and CYP17i-naïve	10/11 (91%)	7/10 (70%)	6/7 (86%)
Post-chemotherapy and CYP17i-naïve	5/9 (56%)	4/7 (57%)	7/10 (70%)
Post-CYP17i	5/11 (45%)	9/15 (60%)	6/11 (55%)

<sup>†</sup>Complete plus partial responses (Response Evaluation Criteria in Solid Tumors, version 1.1).  
<sup>‡</sup>According to Prostate Cancer Working Group criteria.  
CYP17i: Cytochrome P450 17A1 inhibitor; PSA: Prostate-specific antigen.

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-naïve and CYP17 inhibitor-naïve, post-chemotherapy and CYP17 inhibitor-naïve, and post-CYP17 inhibitor.

A PSA response, defined as a ≥50% reduction in serum PSA from baseline at week 12, was observed with all three doses of ODM-201, indicating AR inhibition (TABLE 1) [26]. When patients were divided according to previous treatment, there was an observational trend to higher responses in those who were naïve to both chemotherapy and CYP17 inhibitors and in those who had previously received chemotherapy but not CYP17 inhibitors, compared with patients previously treated with CYP17 inhibitors (TABLE 1).

The highest PSA response was noted with 1400 mg/day of ODM-201 in patients naïve to both chemotherapy and CYP17 inhibitors.

Secondary outcomes, that is, objective response in soft tissue assessed by Response Evaluation Criteria in Solid Tumors (version 1.1) and bone disease stabilization assessed using Prostate Cancer Working Group-2 criteria [29], are shown in TABLE 1 [26]. There were no clear differences by ODM-201 dose

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.

Further supportive efficacy data are available from the Phase I ARAFOR trial [30], in which men with chemotherapy-

naïve and CYP17 inhibitor-naïve 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-naïve and CYP17 inhibitor-naïve 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 (FIGURE 2). Follow-up of patients in both ARADES and ARAFOR is ongoing.

#### 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.

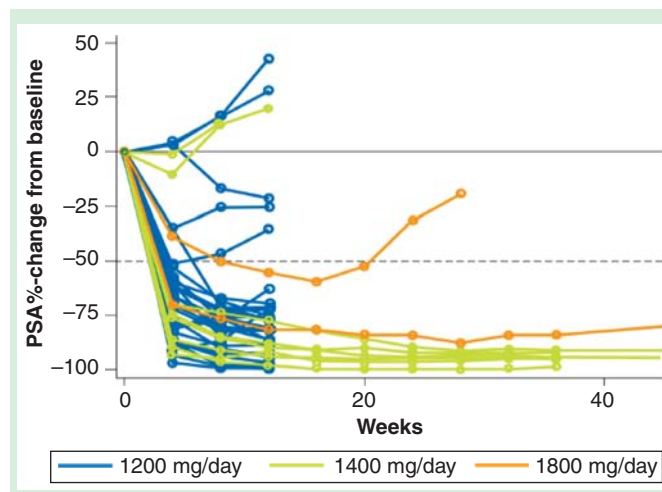
Most events were deemed by the investigators to be related to prostate cancer rather than ODM-201 [26]. Adverse events which were considered to be drug related occurred in 44 (35%) patients, and included fatigue or asthenia in 15 (12%), hot flushes in 6 (5%), decreased appetite in 5 (4%), diarrhea in 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



**Figure 2. PSA changes over time in chemotherapy-naïve and CYP17 inhibitor-naïve patients with metastatic castration-resistant prostate cancer (n = 41): combined analysis of the ARADES and ARAFOR trials [31].**

PSA: Prostate-specific antigen.

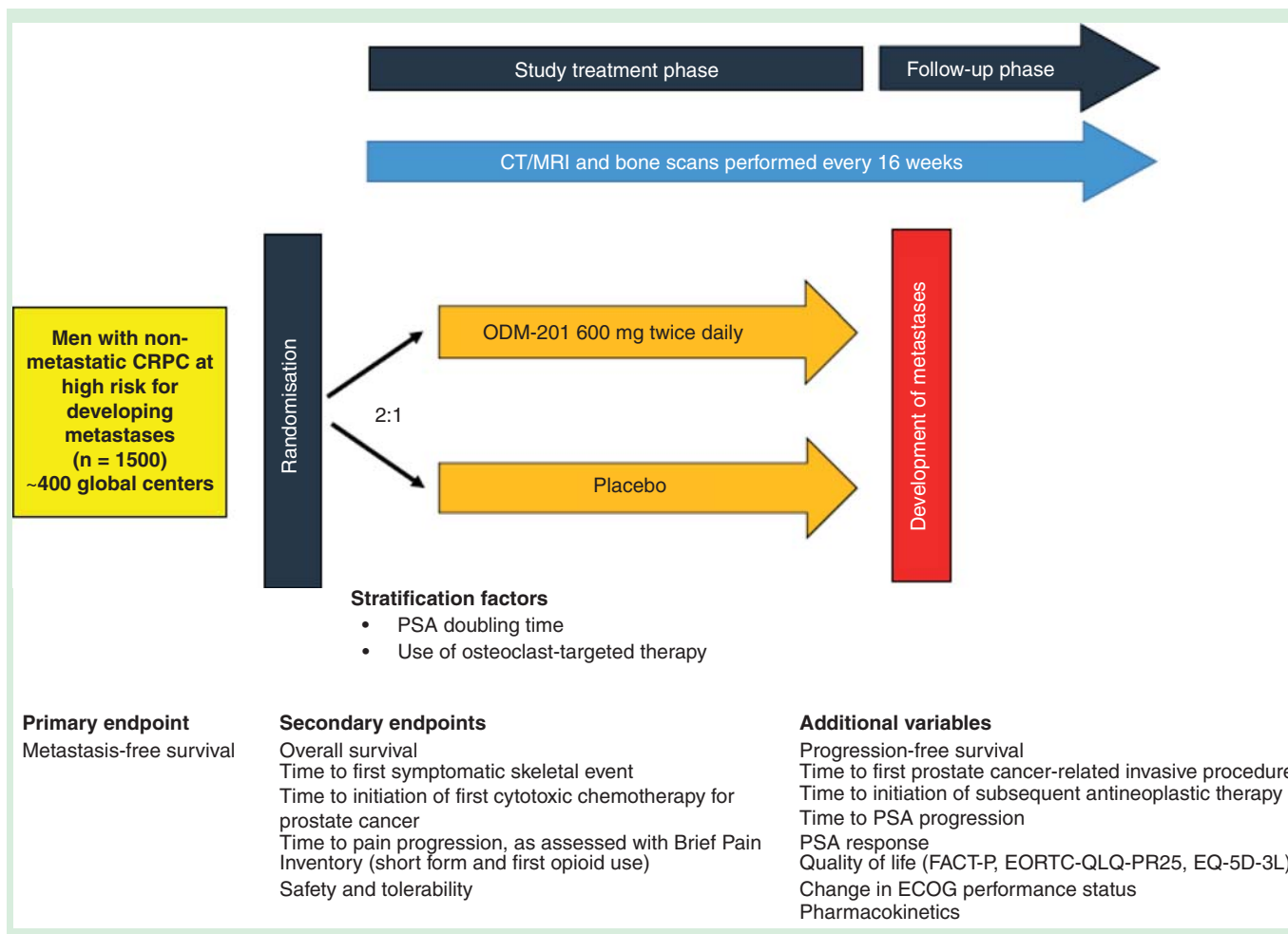
hormonal manipulation in patients with CRPC, a Phase III trial of ODM-201 has recently been initiated in this setting, ARAMIS; clinical trials.gov identifier [38]. A schematic diagram of the design of the ARAMIS trial is shown in FIGURE 3.

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  $\leq 10$  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) [26].**

Adverse event	Grade 1	Grade 2	Grade 3	Total <sup>†</sup>
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%)

<sup>†</sup>Total may be less than the sum of the grade because patients may have had adverse events of several grades.



**Figure 3. ARAMIS trial design.**

CRPC: Castration-resistant prostate cancer; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; EORTC-QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Prostate Cancer module; EQ-5D-3L: EuroQol 5-domain scale; FACT-P: Functional Assessment of Cancer Therapy-Prostate; PSA: Prostate-specific antigen.

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, 5- $\alpha$  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

**Table 3. Ongoing international Phase III randomized trials with androgen receptor inhibitors in men with high-risk (i.e., prostate-specific antigen doubling time  $\leq 10$  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]

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  $\geq 50\%$  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,  $\geq 50\%$  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 AR-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,

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 CHARTED (E3805), reported a progression-free survival benefit with dual therapy, though overall survival was improved only in CHARTED [50,51].

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 [52,53] 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.

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### 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.



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