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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

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Summary

Background ODM-201 is a novel androgen receptor (AR) inhibitor designed to block the growth of prostate cancer cells through high-affi nity binding to the AR and inhibition of AR nuclear translocation. This trial assessed ODM-201's safety, pharmacokinetics, and activity in men with metastatic castration-resistant prostate cancer.

Methods

The ARADES trial is an open-label phase 1–2 trial undertaken in 23 hospitals across Europe and USA with ongoing long-term follow-up. Men with progressive metastatic castration-resistant prostate cancer, who had castrate concentrations of testosterone and an Eastern Cooperative Oncology Group score of 0–1 were enrolled. In the phase 1 part of the trial, patients were given oral ODM-201 at a starting daily dose of 200 mg, which was increased to 400 mg, 600 mg, 1000 mg, 1400 mg, and 1800 mg. In phase 2, patients were randomly assigned centrally and stratifi ed by previous chemotherapy and treatment with CPY17 inhibitors, to receive one of three daily doses of ODM-201 (200 mg, 400 mg, and 1400 mg). The primary endpoint in phase 1 was safety and tolerability, whereas in phase 2 it was the proportion of patients with a PSA response (50% or greater decrease in serum PSA) at week 12. All analyses included patients who had received at least one dose of ODM-201. This trial is registered with ClinicalTrials.gov, number NCT01317641, and NCT01429064 for the follow-up after 12 weeks.

Findings

We enrolled patients between April 5, 2011, and March 12, 2013. In phase 1, 24 patients were enrolled to six sequential cohorts of three to six patients and received a daily dose of ODM-201, 200–1800 mg. No dose-limiting toxic eff ects were reported and the maximum tolerated dose was not reached. In phase 1, three patients reported eight adverse events of grade 3 (fracture, muscle injury, laceration, paralytic ileus, pain, presyncope, urinary retention, and vomiting) and one patient had a grade 4 adverse event (lymphoedema). None of the grade 3–4 adverse events were deemed to be related to ODM-201. Of the phase 1 patients, the four who received 200 mg, seven who received 400 mg, and three who received 1400 mg entered the phase 2 part of the trial. In addition to these patients, 110 were randomly assigned to three groups: 200 mg (n=38), 400 mg (n=37), and 1400 mg (n=35). For these patients, the most common treatment-emergent adverse events were fatigue or asthenia (15 [12%] of 124 patients), hot fl ush (six [5%]), and decreased appetite (fi ve [4%]). One patient (<1%) had a grade 3 treatment-emergent adverse event (fatigue); no patients had a treatment-emergent grade 4 adverse event. 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. 11 (29%) patients in the 200 mg group, 13 (33%) in the 400 mg group, and 11 (33%) in the 1400 mg group had a PSA response at 12 weeks. Interpretation Our results suggest that ODM-201 monotherapy in men with progressive metastatic castration-resistant prostate cancer provides disease suppression and that ODM-201 has a favourable safety profi le. These fi ndings support further investigation of clinical responses with ODM-201 in men with castration-resistant prostate cancer.

Introduction

Prostate cancer is the most common cancer in European men, accounting for an estimated 416 700 new diagnoses every year (23% of all new cancer cases in men) and is a leading cause of cancer-related deaths (estimated 92 200 deaths per year).[1] Most patients with advanced prostate cancer are initially treated with androgen-deprivation therapy via orchiectomy or a luteinising hormone-releasing hormone (LHRH) agonist or antagonist .[2,3] However, despite castrate levels of serum testosterone, nearly all men with advanced disease eventually develop metastatic castration-resistant prostate cancer. Until recently, treatment options with proven efficacy for patients with this disorder were limited to docetaxel plus prednisone and zoledronate. However, several new treatment options with different mechanisms of action have recently become available, including abiraterone acetate (abiraterone),[4] sipuleucel-T,[5] cabazitaxel,[6] denosumab,[7] enzalutamide,[8] and radium (223Ra) dichloride.[9] Metastatic castration-resistant prostate cancer is associated with continued expression of the androgen receptor (AR), and tumour growth remains dependent on AR signalling.[10,11] Several treatments targeting the AR axis such as abiraterone and enzalutamide have shown improved survival in metastatic castration-resistant prostate cancer.[4, 8,12] The mechanisms behind continued AR signalling in metastatic castration-resistant prostate cancer can include adrenal or intratumoural androgen synthesis, increased AR expression due to gene amplification or other mechanisms, and constitutive AR activation due to splice variants or activating mutations.[10,13] Other identified mechanisms of resistance to castration include indirect activation via non-AR pathways and cell cycle activation.[14] Recently, a Phe876Leu missense mutation in the ligand-binding domain of AR has been described. This mutation confers resistance to enzalutamide and ARN-509 in LNCaP cell lines overexpressing wild-type AR as models of prostate cancer.[15]

In the past decade, several second-generation AR inhibitors, such as enzalutamide,[16] have been developed to provide improved mechanisms of action. ODM-201 is a novel, new-generation AR inhibitor that is structurally distinct from enzalutamide and was selectively developed for the treatment of castration-resistant prostate cancer.[17,18,19] ODM-201 is a mixture (1:1) of two pharmacologically active diastereomers: ORM-16497 and ORM-16555. ODM-201 (both diastereomers) and its major metabolite, ORM-15341, have a

higher AR-binding affinity than do bicalutamide, enzalutamide, and ARN-509.[18,19] Additionally, ODM-201 inhibits nuclear translocation of AR in AR-overexpressing cells and significantly inhibits tumour growth in the murine VCaP CRPC xenograft model. Non-clinical data have also shown negligible penetrance of ODM-201 through the blood–brain barrier, thus suggesting a low risk of seizure.[18,19]

On the basis of promising preclinical data, we started a phase 1–2 clinical trial (ARADES) to assess ODM-201 in men with progressive metastatic castration-resistant prostate cancer. The primary objectives of the phase 1–2 trial were to assess safety and tolerability and to define a maximum tolerated dose. Secondary objectives were to assess the pharmacokinetics of ODM-201 and to assess the antitumour activity of ODM-201 as identified by changes in serum prostate-specific antigen (PSA), by imaging of soft tissue and bone lesions, and by changes in circulating tumour cell counts.

Methods

Patients

ARADES was an open-label, multicentre trial with a non-randomised phase 1 dose escalation portion, a phase 2 randomised dose expansion, and long-term follow-up. Patients were enrolled at 23 hospitals in Europe and the USA. Eligible men aged 18 years or older had histologically confirmed adenocarcinoma of the prostate and progressive metastatic disease despite ongoing androgen-deprivation therapy (LHRH analogue or antagonist, which was continued throughout the treatment, or orchiectomy) with serum testosterone concentrations lower than 0·50 ng/mL (<1·7 nmol/L). We defined disease progression in soft-tissue by modified Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) or in bone by two or more new lesions identified by radionuclide bone scan or a rising PSA. The criteria for rising PSA was PSA higher than 2 ng/mL in at least two successive rising measurements, taken at least 1 week apart. Patients had to have received previous first generation antiandrogen treatment, had antiandrogen withdrawal, and up to two previous chemotherapy regimens. Other eligibility criteria were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and no previous therapy with enzalutamide or an investigational AR inhibitor. We did not exclude patients with a history or risk of seizure. The appendix shows full inclusion and exclusion criteria.

The trial was approved by the investigational review board or independent ethics committee of each participating centre, and competent authorities. The trial was done according to the principles of the Declaration of Helsinki and in compliance with guidelines for Good Clinical Practice. All patients provided written informed consent.

Randomisation and masking

The treatment allocation lists were created and randomisation was done centrally at Orion Corporation Orion Pharma. For the phase 1 dose-escalation part of the study, no randomisation was done. The patients entered the phase 1 in the order we found them to be eligible. In the phase 2, before the third expanded dose level was determined, patients were randomly assigned (ratio 1:1) by blocks of four and two to 200 mg or 400 mg daily doses of ODM-201 with previous treatment (chemotherapy-naive and CYP17 inhibitor-naive; post-chemotherapy and CYP17 inhibitor-naive; and post-CYP17 inhibitor) as stratification factors. Once we had identified the third expanded dose level, patients were randomly assigned to 200 mg, 400 mg, or 1400 mg daily doses, at an allocation ratio that accounted for how many blocks were already used, with the three previous treatments as stratification factors.

Procedures

In the open-label phase 1 part, sequential dose-escalation cohorts of three to six patients were given oral ODM-201 (with food twice daily, eg, 200 mg daily dose=100 mg twice a day) at a starting daily dose of 200 mg, which was increased to 400 mg, 600 mg, 1000 mg, 1400 mg, and 1800 mg.

Patients who did not experience dose-limiting toxicity (DLT), defined as treatment-related toxic effects of grade 3 or higher, within the first 28 days were permitted to continue ODM-201 treatment in the absence of disease progression or any intolerable adverse events. We did not permit any intrapatient dose escalation. The next dose level was started after a minimum of three patients had completed 28 days of treatment and after safety review by the independent data and safety monitoring board.

The phase 2 part included three expanded cohorts (200 mg, 400 mg, and 1400 mg daily dose) each containing about 35 patients. We selected the 200 mg and 400 mg daily doses as the two lower dose levels for the phase 2 part while dose escalation was ongoing in the phase 1 part, based on at least 50% PSA response, good tolerability, and the pharmacokinetics noted at these doses. After completion of the phase 1 dose escalation, we selected the dose of 1400 mg daily as the third dose for phase 2 on the same basis as the other dose levels.

We classified adverse events by system organ classes and preferred terms (Medical Dictionary for Regulatory Activities coding system) and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03). A central ECG laboratory recorded and read electrocardiograms, using a 12-lead Holter system (in the 1400 mg and 1800 mg dose-escalation cohorts). We did laboratory assessments (haematology, serum chemistry, hormones, and urine tests) at baseline, once a week for the first 28 days, then every 4 weeks until 9 months and every 3 months thereafter, plus at the end-of-study visit.

We did PSA measurements every 4 weeks until 9 months, and every 3 months thereafter. We assessed changes in serum PSA as percentage change in PSA at 12 weeks from baseline. PSA was analysed centrally, and we only used these central values for the analyses. We assessed soft-tissue response using modified RECIST (version 1.1) in chest, abdomen, and pelvic CT or MRI scans, done at baseline, week 12, and every 3 months thereafter. We assessed bone disease by changes in lesions on bone scans done at baseline, week 12, and every 3 months thereafter; we defined progression by the appearance of two or more new lesions compared with a previous scan. There was a 12-week minimum treatment period before PSA or radiological progression was declared. We measured circulating tumour cell count per 7·5 mL of blood using the CellTracks system (CellSearch assay, Veridex, NJ, USA) from blood samples obtained at baseline and week 12. We defined median time to PSA progression as the time from start of ODM-201 treatment until documentation of a 25% increase or higher and an absolute increase of 2 ng/mL or higher in PSA from the nadir (Prostate Cancer Working Group [PCWG2] criteria)[20] and also as the time from start of ODM-201 treatment until documentation of a 25% increase or higher in PSA from baseline, representing an absolute increase of at least 2 ng/mL.
We obtained blood samples for the pharmacokinetics analyses. We identified plasma concentrations of diastereomers ORM-16497 and ORM-16555, and the major metabolite ORM-15341 by liquid chromatography–tandem mass spectrometry (LC-MS/MS); ODM-201 concentration was the sum of ORM-16497 and ORM-16555 concentrations.

Outcomes

In phase 1, the primary outcome was safety and tolerability of ODM-201 including the frequency and severity of adverse events, plus any clinically significant changes in vital signs, electrocardiographs, and laboratory values. The secondary outcome was the pharmacokinetics of ODM-201.

In phase 2, the primary outcome was PSA response at week 12, defined as a decrease of 50% or more in serum PSA from baseline. Secondary outcomes were the objective disease response, as assessed by RECIST for soft tissue and by PCWG2 criteria for bone, time to PSA progression analysed using PCWG2 criteria, and time to radiographic disease progression by RECIST and PCWG2 criteria.

Statistical analysis

Activity and safety were assessed in a population that consisted of all patients who received at least one dose of ODM-201 treatment. The pharmacokinetic population consisted of patients who had no major protocol violations affecting pharmacokinetic outcomes and had a sufficient number of data points for the pharmacokinetic variables to be determined. We used this population for all pharmacokinetic analyses. PSA response rate is presented as a percentage of patients with a response at week 12 with the corresponding 95% CI based on the binomial distribution. We used the Kaplan-Meier method to estimate the progression curves. We did not deem early increases in PSA before 12 weeks to be PSA progression. We summarised all safety and secondary outcomes descriptively. We did all analyses with SAS for Windows, version 9.4. For the phase 2 part, a sample size of eight assessable patients per dose in each stratification group would provide 80% confidence to reject a PSA response rate of 55% or less at a 1-sided significance level of 0·2, assuming a true PSA response rate of 70%. This trial and its follow-up are registered with ClinicalTrials.gov, number NCT01317641 for the trial and NCT01429064 for its follow-up.

Role of the funding source

The trial funders contributed to the design, conduct, analysis, and interpretation of the data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

We enrolled patients from April 5, 2011, to March 12, 2013. Altogether 201 patients were screened and 136 enrolled (24 were enrolled in the dose-escalation phase and 112 randomly assigned to receive either 200 mg, 400 mg, or 1400 mg of ODM-201; figure 1). Two patients who were randomly assigned to treatment did not start ODM-201, and were therefore excluded from efficacy and safety analyses. Of the phase 1 patients, four who received 200 mg, seven who received 400 mg, and three who received 1400 mg entered the phase 2 part of the trial, bringing the total number of patients at expanded dose levels assessed for activity and safety to 124 patients and the number assessed for safety to 134 patients (all dose levels, appendix). The cutoff date for the data included in this report was Oct 4, 2013. The median time on ODM-201 treatment was 24·8 months (IQR 24·8–25·2) in the phase 1 and 11·0 months (IQR 8·3–14·0) in the phase 2. Altogether, 76 (57%) of 134 patients continued treatment for more than 12 weeks, and 36 (27%) of 134 patients were still receiving ODM-201 treatment at the time of data cutoff (Oct 4, 2013). The most common reason for discontinuation was disease progression, and only five (4%) of 124 patients discontinued because of an adverse event. Investigators at study sites did not deem these adverse events leading to discontinuation to be related to ODM-201. No dose reductions were required for any patient.

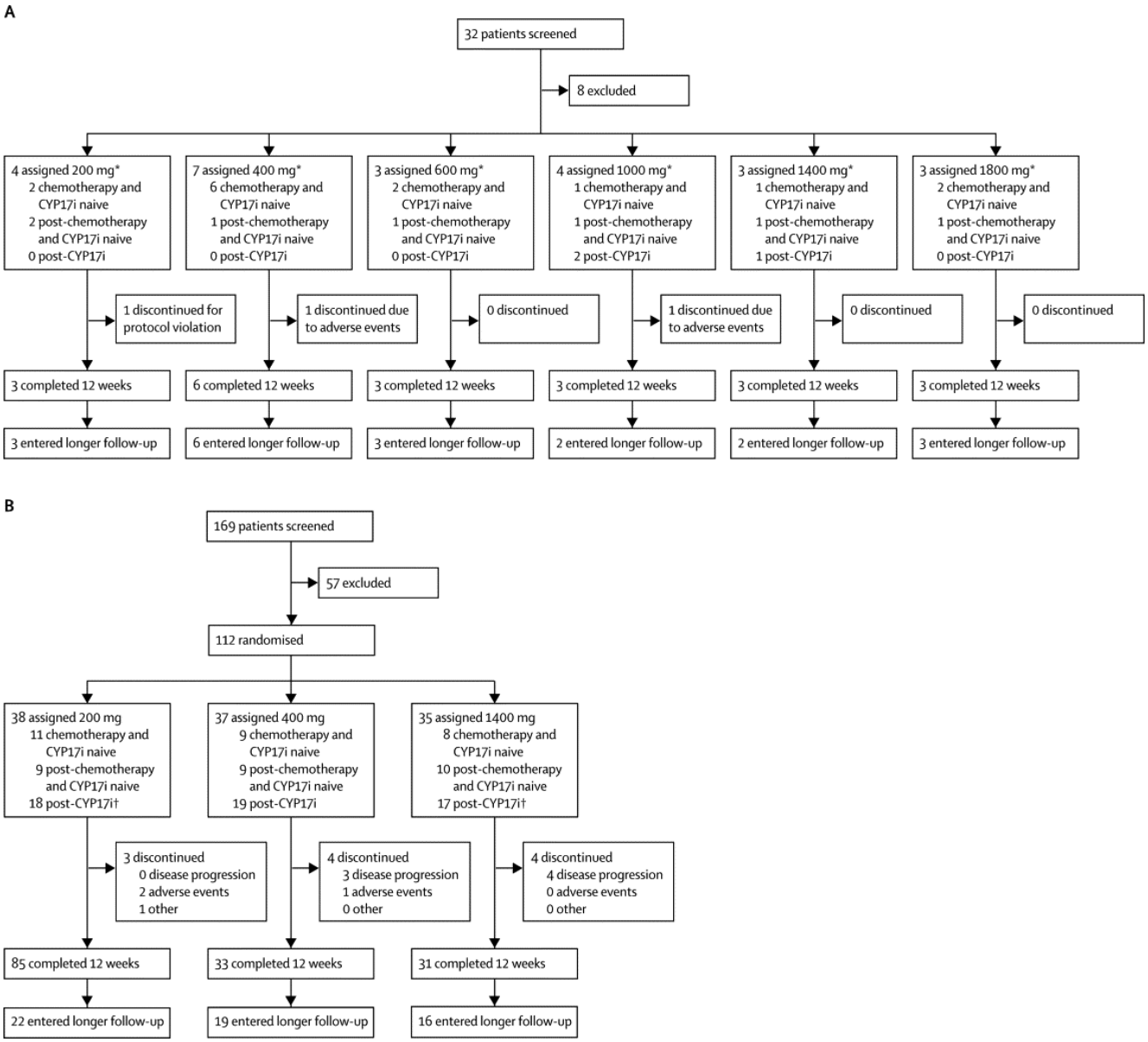


Figure 1.

Trial profile

(A) Phase 1. (B) Phase 2. *Included in phase 2 analyses of safety and efficacy. †One patient not treated.

Table 1 shows the baseline characteristics of 24 patients enrolled in the phase 1 dose escalation part. ODM-201 was tolerated up to the highest pre-specified dose level of 1800 mg, and the maximum tolerated dose was not reached. Most adverse events (116 [93%] of 125) were grade 1–2. The most common adverse events were fatigue or asthenia in ten (42%) of 24 patients, diarrhoea in seven (29%) patients, arthralgia in six (25%) patients, back pain in six (25%) patients, and headache in five (21%) patients. Three (13%) patients reported eight adverse events of grade 3 (fracture, muscle injury, laceration, paralytic ileus, pain, presyncope, urinary retention, and vomiting) and one (4%) patient had a grade 4 adverse event (lymphoedema). None of the grade 3–4 adverse events were deemed to be related to ODM-201. Two (8%) patients discontinued treatment because of adverse events (bone pain and severe infection). No dose-limiting toxic effects were reported and no dose-related trends were noted for any adverse events.

Table 1. Baseline characteristics	**Phase 1 (n=24)**	**Phase 2**		
		200 mg group (n=38)	400 mg group (n=37)	1400 mg group (n=35)
Age (years)	69 (64–74)	67 (65–73)	68 (64–75)	73 (64–78)
PSA (ng/mL)	27 (13–96)	109 (43–352)	95 (45–255)	155 (31–382)
LDH (U/L)	249 (192–412)	220 (195–292)	232 (202–322)	226 (201–322)
Albumin (g/L)	38 (36–44)	38 (35–42)	38 (36–41)	41 (35–44)
Chemotherapy-naive and CYP17 inhibitor-naive	14 (58%)	11 (29%)	9 (24%)	8 (23%)
Post-chemotherapy and CYP17 inhibitor-naive	7 (29%)	9 (24%)	9 (24%)	10 (29%)
Post-CYP17 inhibitor	3 (13%)	18 (47%)	19 (51%)	17 (49%)
Previous lines of chemotherapy	10 (42%)	24 (63%)	25 (68%)	21 (60%)
One line	9 (38%)	20 (53%)	23 (62%)	18 (51%)
Two lines	1 (4%)	4 (11%)	2 (5%)	3 (9%)
Total Gleason score at diagnosis				
<8	15 (68%)	15 (42%)	20 (59%)	15 (46%)
≥8	7 (32%)	21 (58%)	14 (41%)	18 (55%)
Missing*	2	2	3	2
Initial therapy				
Prostatectomy	6 (25%)	5 (13%)	8 (22%)	2 (6%)
Orchiectomy	1 (4%)	3 (8%)	1 (3%)	2 (6%)
Medical castration	9 (38%)	23 (61%)	16 (43%)	18 (51%)
Radiotherapy	3 (13%)	3 (8%)	10 (27%)	7 (20%)
Other	5 (21%)	4 (11%)	2 (5%)	6 (17%)
Time from diagnosis to start of ODM-201 treatment (months)	86 (10–231)	53 (40–90)	74 (35–113)	57 (29–100)
Previous hormonal therapy				
Ketoconazole	3 (13%)	3 (8%)	0	1 (3%)
GnRH	24 (100%)	36 (95%)	35 (95%)	32 (91%)
First generation antiandrogen	24 (100%)	38 (100%)	37 (100%)	35 (100%)
One line	9 (38%)	23 (61%)	26 (70%)	25 (71%)
>one line	15 (62%)	15 (39%)	11 (30%)	10 (29%)
Oestrogens	7 (29%)	4 (11%)	5 (14%)	6 (17%)
ECOG performance status				
0	17 (71%)	19 (50%)	20 (54%)	16 (46%)
1	7 (29%)	19 (50%)	17 (46%)	19 (54%)
Circulating tumour cell count				
<5 cells per 7·5 mL of blood	13 (54%)	18 (47%)	18 (49%)	16 (46%)
≥5 cells per 7·5 mL of blood	9 (38%)	17 (45%)	17 (46%)	14 (40%)
NA	2 (8%)	3 (8%)	2 (5%)	5 (14%)
Disease localisation				
Bone disease	15 (63%)	34 (89%)	32 (86%)	32 (91%)

	Bone only	6 (25%)	12 (32%)	11 (30%)	20 (57%)
	Bone and soft tissue	9 (38%)	22 (58%)	21 (57%)	12 (34%)
	Soft-tissue disease	17 (71%)	26 (68%)	26 (70%)	15 (43%)
	Lymph node	17 (71%)	18 (47%)	24 (65%)	7 (20%)
	Visceral	1 (4%)	10 (26%)	8 (22%)	8 (23%)
	No radiological evidence of metastases	1 (4%)	0	0	0
Bone metastases					
	0	9 (38%)	6 (16%)	5 (14%)	3 (9%)
	1–4	3 (13%)	10 (26%)	13 (35%)	6 (17%)
	5–20	7 (29%)	11 (29%)	9 (24%)	8 (23%)
	>20‡	5 (21%)	11 (29%)	10 (27%)	18 (51%)

Data are number of patients (%) or median (IQR). PSA=prostate-specific antigen. LDH=lactate dehydrogenase. GnRH=gonadotropin-releasing hormone. ECOG=Eastern Cooperative Oncology Group. NA=not assessable.
*Gleason score not available. †Or non-countable (one in phase 1 and 28 in phase 2).

In the pharmacokinetic analysis, ODM-201 was rapidly absorbed and the median tmax were 3.0–5.1 h for ODM-201 and 1·5–5·0 h for ORM-15341 on day 1. The mean metabolite:parent ratio (area under the curve, AUC) at steady state was 1.6–2.3:1. The exposure of ODM-201 (AUCt and Cmax) at steady state increased in a linear, dose-related manner up to 1400 mg daily dose (figure 2). Exposure was similar after the 1800 mg daily dose compared with after the 1400 mg daily dose. Dose escalation was discontinued because of a plasma concentration plateau of ODM-201. Steady-state plasma concentrations were reached after 1 week of continuous treatment, with no increase noted between 2 and 4 weeks. The mean half-life of ODM-201 was independent of dose, being 15·8 h (SD 13·8) at steady state after 200–1800 mg daily doses. The mean half-life of ORM-15341 was 10·0 h (3·8) at steady state after 200–1800 mg daily doses.

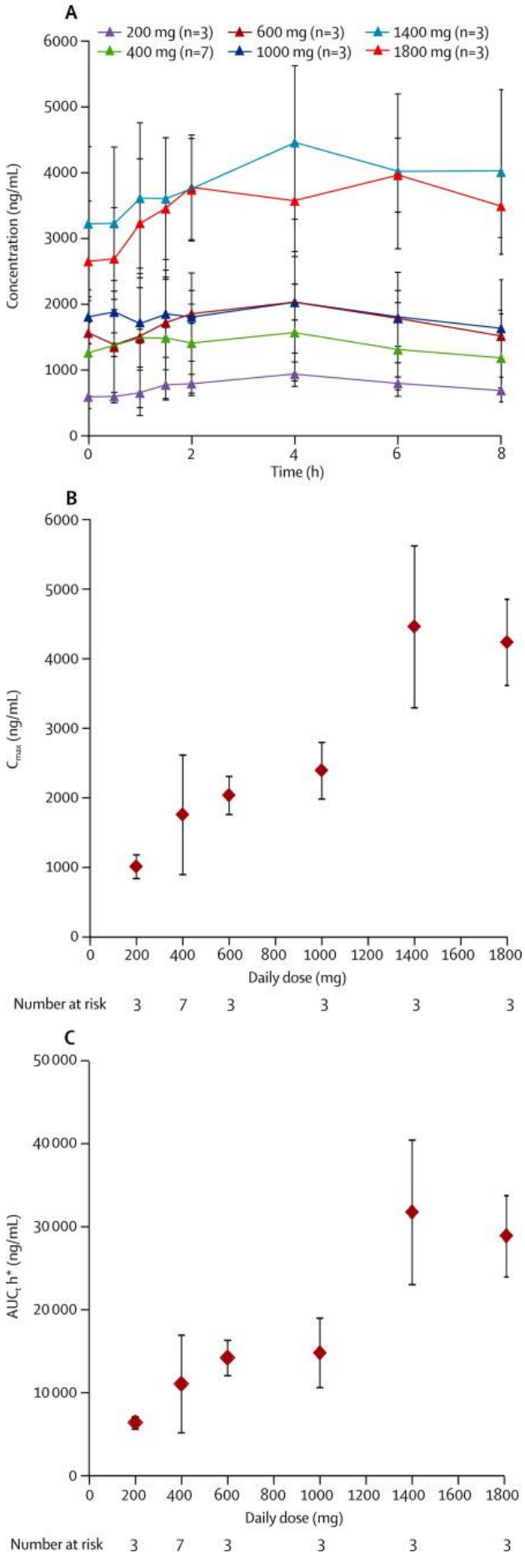


Figure 2. Pharmacokinetics of ODM-201 at steady state in the phase 1 population. (A) Mean steady state concentrations of ODM-201. (B) ODM-201 mean C_{max} by dose. (C) ODM-201 mean area under the curve by dose. Datapoints are means and whiskers depict SDs

Anticancer activity was noted across all of the six doses. We noted a PSA response (reduction of at least 50% in serum PSA) in 17 (71%) patients at 12 weeks, when including the three patients without a PSA sample who were discontinued before the 4-week visit in phase 1 (one in each 200 mg, 400 mg, and 1000 mg dose group). A PSA response was noted in 17 (81%) of the 21 patients who had PSA samples at baseline and week 12. Additionally, in 31 evaluable patients, an early response to ODM-201 was noted based on similar 50% or higher reduction in PSA at weeks 4 across all levels (n=15, 71%) and 8 (n=16, 80%).

Table 1 shows the baseline characteristics of patients enrolled in the phase 2 part of the study. Characteristics by previous treatment regimens are shown in the appendix. ODM-201 was well tolerated in all expanded cohorts (table 2). The appendix shows the adverse events for the total safety population including all dose levels. Most adverse events (728 [91%] of 796) were grade 1–2. The most common adverse events (all grades)were fatigue or asthenia in 38 (31%) of 124 patients, back pain in 26 (21%) patients, arthralgia in 19 (15%) patients, pain in 18 (15%) patients, and constipation in 17 (14%) patients (one patient could have had adverse events of several grades). No differences were observed between groups when examined by dose or by previous treatment. The investigators deemed most adverse events to be related to prostate cancer. Adverse events related to ODM-201 (by investigator's judgment) were reported in 44 (35%) patients, including fatigue or asthenia in 15 (12%) patients, hot flush in six (5%) patients, decreased appetite in five (4%) patients, diarrhoea in three (2%) patients, and headache in three (2%) patients. No seizures were noted during the trial. Adverse events of grade 3 were reported in only 27 (22%) patients and adverse events of grade 4 in two (<2%) patients. No grade 4 adverse events and only one grade 3 adverse event (fatigue or asthenia) were deemed to be related to ODM-201. Four (3%) patients died because of progression of prostate cancer, of which three died within 30 days after ODM-201 was discontinued. Three (2%) patients discontinued the trial because of adverse events (fatigue, cauda equina syndrome, and colitis). None of these discontinuations were deemed related to ODM-201.

Table 2. Adverse events occurring in 5% or more patients: expanded dose levels, safety population (n=124)

	Grade 1	Grade 2	Grade 3
Fatigue or asthenia	27 (22%)	13 (10%)	2 (2%)
Back pain	16 (13%)	13 (10%)	2 (2%)
Arthralgia	15 (12%)	9 (7%)	2 (2%)
Pain	8 (6%)	8 (8%)	2 (2%)
Constipation	14 (11%)	5 (4%)	0
Decreased appetite	15 (12%)	1 (<1%)	0
Nausea	12 (10%)	4 (3%)	0
Peripheral oedema	13 (10%)	2 (2%)	0
Insomnia	7 (6%)	6 (5%)	1 (<1%)
Musculoskeletal pain	9 (7%)	3 (2%)	0
Anaemia	0	8 (6%)	3 (2%)
Diarrhoea	9 (7%)	0	0
Vomiting	8 (6%)	0	1 (<1%)
Weight loss	8 (6%)	1 (<1%)	0
Hot flush	6 (5%)	3 (2%)	0
Muscular weakness	4 (3%)	3 (2%)	1 (<1%)
Hypertension	1 (<1%)	7 (6%)	1 (<1%)
Pain in extremity	5 (4%)	4 (3%)	0
Headache	5 (5%)	1 (<1%)	1 (<1%)

Dyspnoea	5 (4%)	1 (2%)	0
Urinary tract infection	7 (6%)	0	0

Data are number of patients (%).

We noted a PSA response (≥ 50% decrease in PSA) by week 12 with all doses and all treatment groups, but significantly fewer were seen in patients previously treated with CYP17 inhibitors than in those who were naïve to both chemotherapy and CYP17 inhibitors, and those who had previously received chemotherapy but not CYP17 inhibitors (figure 3 and table 3). We noted the best PSA responses at 1400 mg in patients naive to both chemotherapy and CYP17 inhibitor (table 3). Eight patients (22%) who were naive to both chemotherapy and CYP17 inhibitor, seven (22%) who had been treated with chemotherapy but not CYP17 inhibitors, and 30 (55%) in who had received a CYP17 inhibitor did not have a decrease in PSA during the first 12 weeks. No clear dose response was noted in CYP17 inhibitior-naive patients previously treated with chemotherapy and in patients who received CYP17 inhibitor. The appendix shows percentage change in PSA at weeks 4, 8, and 12 from baseline.

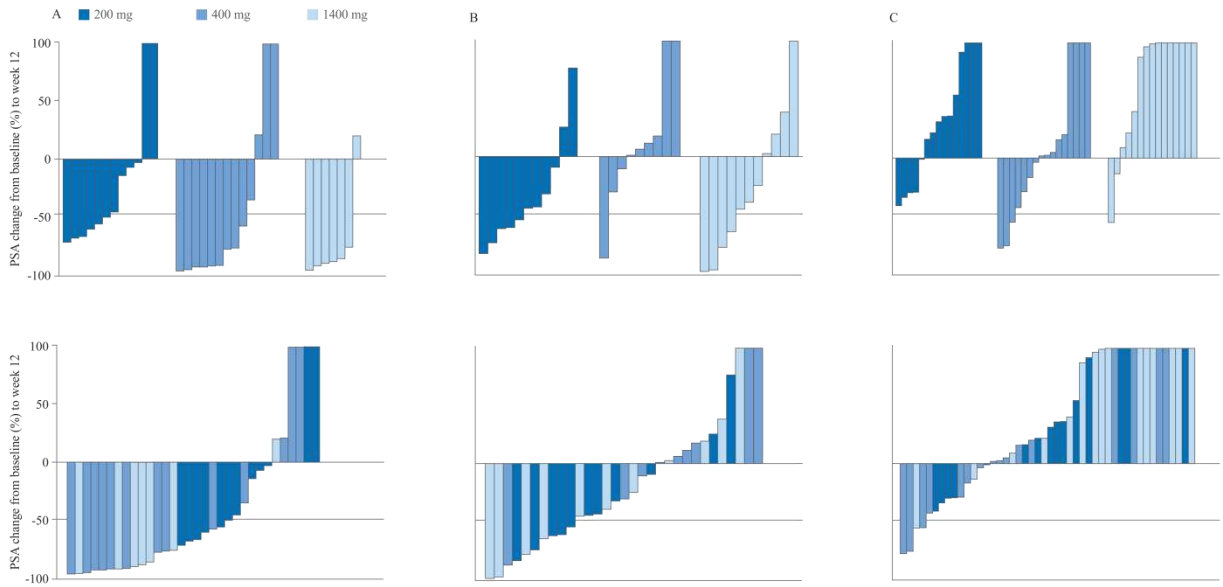


Figure 3.

Percentage change in PSA at week 12 from baseline.

(A) Chemotherapy-naive and CYP17i-naive patient group. (B) Post-chemotherapy and CYP17i-naive patient group. (C) Post-CYP17i patient group. Includes patients carried forward from phase 1.

PSA=prostate-specific antigen. CYP17i=cytochrome P450 17A1 inhibitor. *Data truncated at 100%.

Table 3.
PSA decreases from baseline at 12 weeks: expanded dose levels

	200 mg group	400 mg group	1400 mg group
Chemotherapy-naive and CYP17i-naive			
Number of evaluable patients	12	13	7
≥90%	0	6 (46%)	3 (43%)
≥50%	6 (50%)	9 (69%)	6 (86%)
≥30%	7 (58%)	10 (77%)	6 (86%)
Post-chemotherapy and CYP17i-naive			
Number of evaluable patients	11	9	11
≥90%	0	0	2 (18%)
≥50%	5 (45%)	1 (11%)	4 (36%)

≥30%	8 (73%)	2 (22%)	6 (55%)
Post-CYP17i			
Number of evaluable patients	15	17	15
≥90%	0	0	0
≥50%	0	3 (18%)	1 (7%)
≥30%	4 (27%)	4 (24%)	1 (7%)

CYP17i=cytochrome P450 17A1 inhibitor.

RECIST responses or stable disease in soft tissue, and stabilised disease in bone are shown in table 4. No clear differences in response by dose were noted in soft tissue and bone; although this variable was not formally analysed because of the small number of patients within each dose group and subgroup. The highest activity was noted in patients who were chemotherapy-naive and CYP17 inhibitor-naive patients (table 4). We noted one complete response (17%; 200 mg dose group) and two partial responses (33%; 400 mg and 1400 mg dose groups) in patients who were chemotherapy and CYP17 inhibitor-naive with visceral disease. One partial response (17%; 1400 mg) occurred in a patient who had received chemotherapy but not a CYP17 inhibitor. We did not note any responses in patients with visceral disease who had already received a CYP17 inhibitor.

Table 4.

Imaging results at week 12

		200 mg group	400 mg group	1400 mg group
Chemotherapy-naive and CYP17i-naive (n=37)				
Number of patients with soft tissue evaluable		9	9	2
RECIST response				
	CR+PR	1 (11%)	4 (44%)	1 (50%)
	CR+PR+SD	9 (100%)	6 (67%)	2 (100%)
Number of patients evaluable for bone scan		11	10	7
	No change	10 (91%)	7 (70%)	6 (86%)
Post-chemotherapy and CYP17i naive (n=32)				
Number of patients with soft tissue evaluable		8	7	5
RECIST response				
	CR+PR	1 (13%)	0	1 (20%)
	CR+PR+SD	5 (63%)	3 (20%)	4 (20%)
Number of patients evaluable for bone scan		9	7	10
	No change	5 (56%)	4 (20%)	7 (20%)
Post-CYP17i (n=55)				
Number of patients with soft tissue evaluable		13	12	9
RECIST response				
	CR+PR	0	2 (17%)	0
	CR+PR+SD	5 (38%)	9 (75%)	6 (67%)
Number of patients evaluable for bone scan		11	15	11
	No change	5 (45%)	9 (60%)	6 (55%)

Data are number of patients (%), unless otherwise indicated. CR=complete response. PR=partial response. SD=stable disease. CYP17i=cytochrome P450 17A1 inhibitor.

We measured baseline and 12-week circulating tumour cell results in 87 of 124 patients. Compared with baseline, 41 (82%) patients maintained favourable circulating tumour cell counts (<5 cells per 7·5 mL of blood) at week 12. In the patients with unfavourable counts (≥5 cells per 7·5 mL of blood) at baseline, 14 (38%) converted to favourable counts, and nine (18%) patients converted from favourable to unfavourable. No clear differences in responses between dose levels was noted. When analysed by previous treatment, conversion from unfavourable to favourable counts was seen in seven (58%) patients who were both chemotherapy and CYP17 inhibitor-naive, in seven (58%) of those who had received chemotherapy but not a CYP17 inhibitor, and no patients who had been previously treated with a CYP17 inhibitor. However, 16 (73%) patients who had received a CYP17 inhibitor maintained favourable counts (table 5).

Table 5.

CTC conversion rate at week 12: expanded dose levels

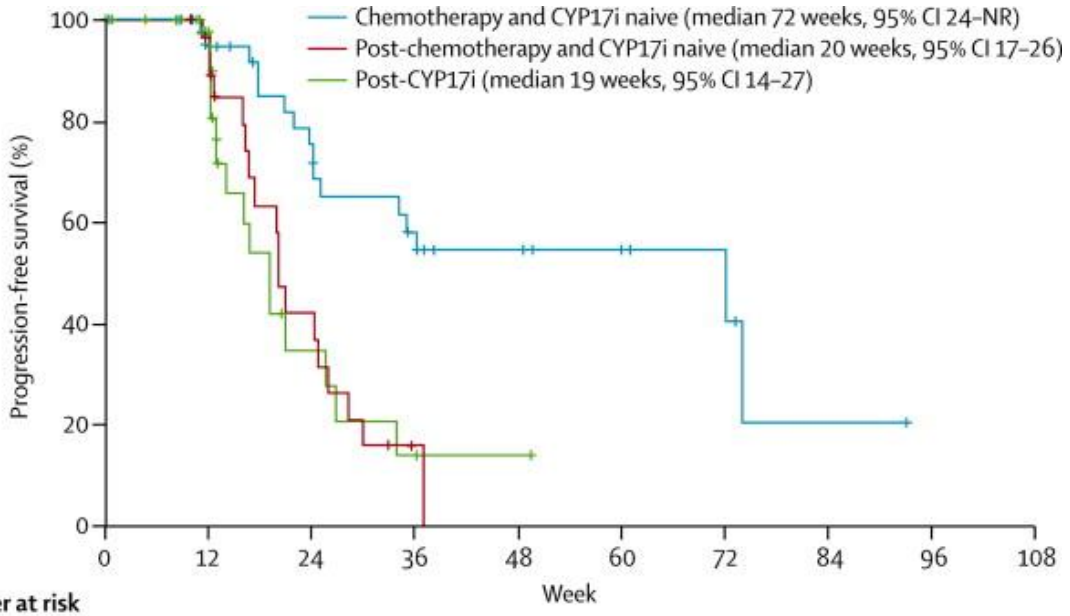
	Chemotherapy-naïve/CYP17i-naive (n=37*)	**Post-chemotherapy/CYP17i-naive (n=32*)**	**Post-CYP17i (n=55†)**
<5 at baseline			
Number of patients	18	16	25
<5 at week 12	15 (88%)	10 (91%)	16 (73%)
≥5 at week 12	2 (12%)	1 (9%)	6 (27%)
NA at week 12	1	5	3
≥5 at baseline			
Number of patients	16	13	24
<5 at week 12	7 (58%)	7 (58%)	0
≥5 at week 12,	5 (42%)	5 (42%)	13 (100%)
NA at week 12	4	1	11

Data are number of patients (%), unless otherwise indicated. CTC=circulating tumour cell. NA=not assessable. CTC count is expressed as cells per 7·5 mL of blood. These data include patients with missing baseline CTC.

*Total number includes three patients with missing baseline.

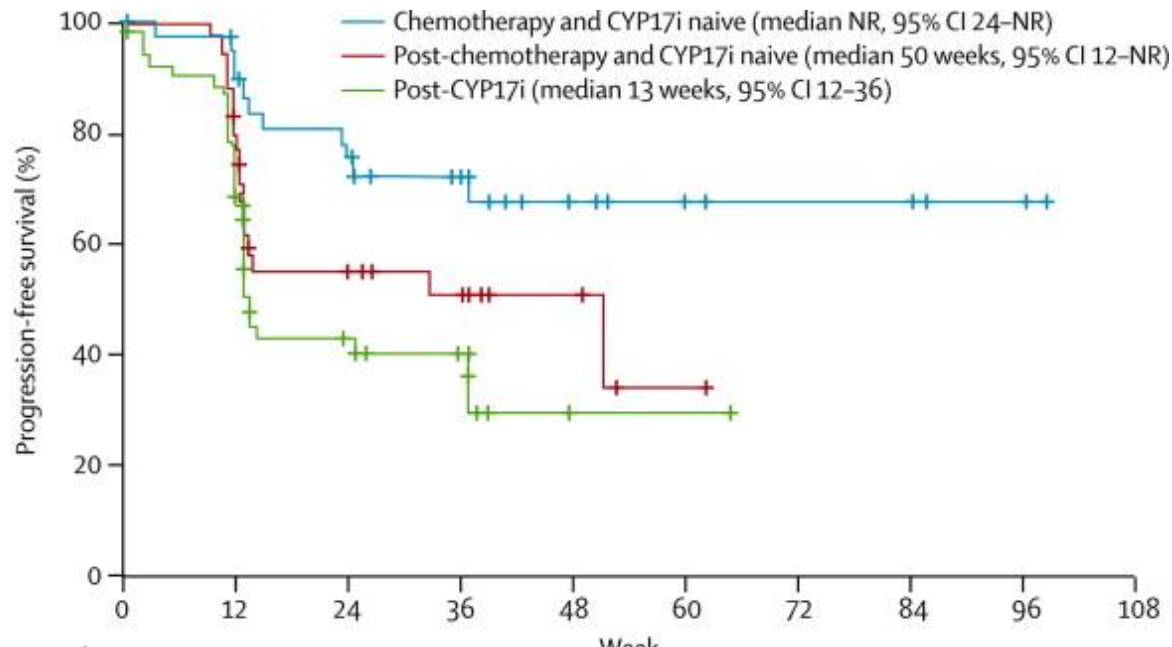
†Total number includes six patients with missing baseline.

Using the PCWG2 criteria[19] of a 25% increase or higher in PSA from nadir, the median time to PSA progression in phase 1–2 (including all dose levels) was 72·3 weeks (95% CI 24·3–not reached [NR]) for patients who were naive to both chemotherapy and 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 (figure 4). Median time to PSA progression, defined as a 25% increase from baseline representing an increase of ≥2 ng/mL, was not reached for any of the subgroups (appendix).



Number at risk									
Chemotherapy and CYP17i naive	42	36	23	16	8	6	4	1	0
Post-chemotherapy and CYP17i naive	35	26	8	1	0				
Post-CYP17i	57	33	5	2	1	0			

Median time to radiological progression was not reached for patients who were naive to both chemotherapy and CYP17 inhibitor (95% CI 36·4–NR); 50·4 weeks (95% CI 12·1–NR) for those who had received chemotherapy but not a CYP17 inhibitor; and 12·7 weeks (95% CI 12·0–36·3) for those who had received a CYP17 inhibitor (figure 5).



Number at risk										
Chemotherapy and CYP17i naive	42	32	25	17	9	5	4	3	1	0
Post-chemotherapy and CYP17i naive	35	23	15	10	3	1	0			
Post-CYP17i	57	31	16	9	1	1	0			

The median serum testosterone level at baseline was 0·4 nmol/L (IQR 0·4–0·6; n=124). Castrate concentrations were maintained at week 12 (0·4 nmol/L [0·4–0·6]; n=111).

Discussion

Findings from this phase 1–2 trial of 134 patients showed that ODM-201 has an encouraging tolerability and anticancer profile in men with metastatic castration-resistant prostate cancer.

ODM-201 was well tolerated up to the highest prespecified daily dose of 1800 mg and a maximum tolerated dose was not reached; no dose-limiting toxic effects were noted and dose escalation was discontinued because of a plasma concentration plateau of ODM-201. Most adverse events were grade 1–2, and the adverse event profile did not differ between dose levels. Many of the noted adverse events (eg, fatigue, diarrhoea, decreased appetite, nausea) might also be deemed disease-related and have been consistently noted in trials of patients with prostate cancer.[6, 8, 21] The overall pattern of tolerability with next-generation AR axis inhibitors is a clear advantage for patients with metastatic castration-resistant prostate cancer, particularly since elderly patients (aged ≥70 years) have the highest probability of developing prostate cancer.[22]

No seizures were noted during this trial. This is in contrast to other recently developed AR inhibitors, which have shown to penetrate the blood–brain barrier in preclinical pharmacokinetic in vivo models, such as ARN-509[23] and enzalutamide.[8,24] In the case of enzalutamide, seizures were reported in three (2%) of 140 patients receiving higher doses of drug (360 mg, 480 mg, 600 mg per day) during a phase 1–2 trial, with seizures also being reported in seven (1%) of 800 patients in the phase 3 AFFIRM trial,[8] which used a lower dose (160 mg/day). In the placebo-controlled phase 3 PREVAIL trial two seizures,[25] one in each treatment group, were reported. Patients with a history or risk of seizure were excluded from these trials, whereas patients with medical history of seizures were allowed to enter the present ARADES trial (three patients had history of seizures). The hypothesis for risk of seizure associated with enzalutamide and ARN-509 is derived from preclinical data showing that both agents bind to and potentially inhibit γ-aminobutyric acid (GABA)-gated chloride channels in the brain.[23,26] The mechanisms underlying the difference between ODM-201 and ARN-509 and enzalutamide are not yet understood, but might be related to the unique chemical structure of ODM-201, which has negligible penetration of the blood–brain barrier in pharmacokinetic studies in mice and in quantitative whole-body autoradiography in rats.[18,19] This hypothesis needs be confirmed in a large phase 3 trial.

Antitumour activity, shown by a reduction of at least 50% in PSA, was noted in all doses and all treatment stratification subgroups. The soft tissue and bone lesion data, as well as time to PSA and radiological progression, provide supportive evidence for the acivity of ODM-201. Furthermore, more than a third of patients converted to favourable circulating tumour cell counts at week 12 and about four-fifths maintained favourable circulating tumour cell counts. No obvious dose-related activity benefits were recorded in the overall population, but the 1400 mg daily dose produced the greatest PSA response rates in patients who had not been previously treated with chemotherapy or CYP17 inhibitors. We noted the highest antitumour activity with ODM-201 in the such patients and the lowest in those who had received CYP17 inhibitors, which is consistent with other reports correlating activity in this patient population.[24, 27] Additionally, the data are consistent with reports of cross-resistance with sequential treatment of enzalutamide and CYP17 inhibitors in metastatic castration-resistant prostate cancer.[28, 29, 30, 31] Because abiraterone and ODM-201 both target the AR axis, the mechanism behind the absence of activity with ODM-201 in patients who have received CYP17 inhibitors might be at the AR level. Patients treated with abiraterone while having progressive disease had increased concentrations of PSA, which could be due to AR activation[32]. On the other hand, AR splice variants[33] and increased steroidogenesis have also been reported to mediate cross-resistance between abiraterone and antiandrogens.[33, 34]

The main limitation of our trial is the open-label, with no control group design, which is typical for phase 1–2 studies. However, this design was sufficient to provide an initial anticancer activity and safety profile of ODM-201, and to inform potential future trial development. Another limitation is that although anticancer activity,

pharmacokinetics, and tolerability were recorded, the quality-of-life measurements were missing from the trial.

In summary, findings from this phase 1–2 trial show that ODM-201 is well tolerated and exhibits high antitumour activity in both chemotherapy-naive patients and chemotherapy-treated patients (panel). Additionally, it further confirms that inhibition of the AR pathway is an effective treatment strategy for patients with progressive metastatic castration-resistant prostate cancer. A phase 3 randomised trial is planned to study ODM-201, at a planned dose of 1200 mg daily, versus placebo in men with non-metastatic castration-resistant prostate cancer.

Panel
Research in context

Systematic review

We did not do a formal systematic review in the planning of this trial. The design of our study was informed by strong evidence that inhibition of androgen receptor (AR) signalling could provide an effective treatment strategy for metastatic castration-resistant prostate cancer (March, 2011). At this time, emerging evidence[10,16] suggested AR overexpression played an important role in the development of metastatic castration-resistant prostate cancer. Additionally, early phase clinical trial data suggested encouraging antitumour activity for initial second-generation AR inhibitors.[24] Therefore, there was interest in pursuing second-generation AR inhibitors as a possible therapeutic strategy in metastatic castration-resistant prostate cancer. We did a comprehensive scientific literature search of PubMed when writing our report in January, 2014, to identify published articles in English with the MeSH terms “Prostatic Neoplasms, Castration-Resistant”; “Receptors, Androgen”; “Clinical Trial, Phase III”; “abiraterone acetate”; “Provenge”; “MDV3100”; “enzalutamide”; “ARN-509”; “cabazitaxel”; “denosumab”; and “radium 223”; we discuss our results in the context of these publications and highlight any notable differences.

Interpretation

Findings from this phase 1–2 analysis show that ODM-201 has encouraging antitumour activity in both chemotherapy-naive patients and chemotherapy-treated men with metastatic castration-resistant prostate cancer. ODM-201 had a favourable safety profile and no seizures were noted. These results support further investigation of ODM-201 in a larger phase 3 trial in men with castration-resistant prostate cancer.

Contributions

KF, CM, AV, LM, PL, JA, and MM contributed to the study concept and design. KF, CM, PB, RJ, VK, NJ, JG, AP, TT, and TE recruited patients to the trial. JA was responsible for statistical analysis. KF, PB, TT, AV, LM, JA, PL, and MM participated in assessment and interpretation of the data. All authors have reviewed and contributed to the final version of this report. The authors take full responsibility for the scope, direction, and content of the report.

Declaration of interests

KF and CM have received consultancy fees from Orion Pharma. PB has received honoria for participation in advisory board meetings of Orion Pharma, GlaxoSmithKline, Pfizer, and Novartis. VK has received payment for speaker bureau from Astellas, Bayer, Roche Finland, Pfizer, MSD, Merck, and Sanofi-Aventis. JG has received consultacy fees from Astellas, Sanofi and Bayer, payment for speaker bureau from Bayer, and reseach grant support paid to his institution from Johnson & Johnson. AP has received honoraria for participation in advisory board meetings of Astellas and Pfizer. TT has received consultancy fees from Orion Pharma, Astellas, Amgen, Sanofi, and Janssen. TE has received consultacy fees and travel support from

Astellas and Janssen. PL was employee of Endo Pharmaceuticals during the conduct of the trial. JA and AV are employees of Orion Corporation Orion Pharma. LM and MM are employees of Orion Corporation Orion Pharma and own stock in Orion Corporation. All other authors declare no competing interests.

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Supplementary appendix.