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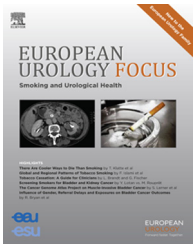


Prostate Cancer

# Safety and Antitumour Activity of ODM-201 (BAY-1841788) in Castration-resistant, CYP17 Inhibitor-naïve Prostate Cancer: Results from Extended Follow-up of the ARADES Trial

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## Abstract

*Background:* Patients with castration-resistant prostate cancer (CRPC) had extended responses to the androgen receptor antagonist ODM-201, in phase 1/2 studies.
*Objective:* To evaluate the safety and antitumour activity of prolonged ODM-201 treatment in patients with CRPC.
*Design, setting, and participants:* The ARADES trial was a multicentre phase 1 (dose escalation) and phase 2 (dose expansion) trial; 134 patients with CRPC were stratified by previous chemotherapy to receive ODM-201. This paper reports extended follow-up in CYP17 inhibitor (CYP17i)-naïve patients.
*Intervention:* Patients ($n = 77$) received oral ODM-201 twice daily at daily doses of 200–1800 mg.
*Outcome measurements and statistical analysis:* Safety, measured as the occurrence of adverse events (AEs), prostate-specific antigen (PSA), and radiographic progression.
*Results and limitations:* The safety profile of extended ODM-201 treatment (median treatment duration 8.2 mo, 95% confidence interval [CI] 5.6–11.0) was consistent with that reported at the time of the original data cutoff in the main ARADES trial, with no unexpected safety concerns over time. The majority of AEs (61.1%) were mild (grade 1); the most common AE was fatigue/asthenia (35.1% of patients), with no clear relationship to ODM-201. Median time to PSA progression was 25.2 mo (95% CI 11.3–25.2) for chemotherapy-naïve men and not reached (NR; 95% CI 5.5–NR) for chemotherapy-pretreated patients; a trend for improved antitumour response was observed for chemotherapy-naïve patients. The median time to radiographic progression was longer for chemotherapy-naïve (14.0 mo, 95% CI 8.1–33.3) than for chemotherapy-pretreated (7.2 mo, 95% CI 2.7–11.0) patients.
*Conclusions:* Prolonged exposure to ODM-201 was well tolerated, with no additional safety concerns; disease suppression was sustained, especially in chemotherapy-naïve patients. These data support further development of ODM-201 in men with CYP17i-naïve CRPC.
*Patient summary:* Extended ODM-201 therapy was well tolerated, with beneficial antitumour activity in men with advanced prostate cancer, indicating that ODM-201 may represent a new active treatment for men with CRPC.
This extension trial is registered at ClinicalTrials.gov (www.clinicaltrials.gov) under identification number NCT01429064.


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## 1. Introduction

Since 1941, when Huggins and Hodges showed that androgen deprivation could inhibit tumour growth in patients with advanced prostate cancer (PCa) [1], targeting of androgen synthesis and the androgen receptor (AR) pathway have formed key therapeutic strategies for the treatment of this cancer [2]. However, as the disease progresses, resistance to long-term androgen ablation develops and the majority of patients progress to castration-resistant prostate cancer (CRPC), which requires subsequent treatment [3,4]. CRPC is associated with poor prognosis and often with increasing levels of serum prostate-specific antigen (PSA), indicating that AR signalling continues to drive the disease [5–7].

The progression of PCa from hormone-sensitive disease has been extensively investigated, and key known mechanisms include AR gene amplification and mutation, AR overexpression, and AR stimulation by non-androgen ligands [8,9]. Therefore, novel second-generation AR antagonists, such as the nonsteroidal AR antagonists ODM-201, apalutamide, and enzalutamide, have been specifically developed for CRPC treatment [6,10,11]. ODM-201 is an investigational oral AR antagonist with a unique chemical structure that is designed to block the growth of cancer cells by binding to the AR with high affinity; this inhibits nuclear translocation and limits the functionality of the receptor. Preclinical studies showed that ODM-201 inhibits the AR more potently than other second-generation antiandrogens such as enzalutamide and apalutamide; it also displayed more potent antitumour activity than enzalutamide in a preclinical model of CRPC characterised by AR amplification and overexpression [12,13].

Evidence from clinical studies suggested that ODM-201 monotherapy provides disease suppression in men with progressive CRPC and is well tolerated [13,14]. The first-in-man phase 1/2 ARADES trial showed that ODM-201 had a positive safety profile in CYP17 inhibitor (CYP17i)-naïve patients (chemotherapy-naïve or post-chemotherapy) and in post-CYP17i patients up to the highest prespecified daily dose of 1800 mg; the maximum tolerated dose was not reached [14]. Most adverse events (AEs) were grade 1–2 and were similar within dose levels (200–1800 mg/d); only 5/124 patients (4%) discontinued treatment because of an AE [14]. In the phase 2 ARADES trial, durable responses were achieved with all doses tested (200, 400, and 1400 mg/d) and were more pronounced in CYP17i-naïve men (both chemotherapy-naïve and chemotherapy-pretreated), than in post-CYP17i patients. Only three patients (2%) discontinued treatment because of AEs, and these were not related to ODM-201 exposure.

As treatment for PCa typically entails prolonged hormonal therapy, sustained treatment should be well tolerated and not result in rapid emergence of acquired resistance to AR antagonists [11]. We analysed the safety and antitumour activity of ODM-201 in CYP17i-naïve patients with advanced CRPC (chemotherapy-naïve or chemotherapy-pretreated) from the extension component of the ARADES trial.

## 2. Patients and methods

### 2.1. Study design and patients

The current trial is an analysis based on extended follow-up of patients enrolled in ARADES, an open-label, multicentre trial with two components: phase 1 (non-randomised dose escalation) and phase 2 (randomised dose expansion). The complete design and methods for ARADES were published previously [14]. In brief, male patients aged $\geq$18 yr with histologically confirmed adenocarcinoma of the prostate and progressive metastatic disease were eligible, provided that their serum testosterone concentration was $<$0.50 ng/ml; they had received prior first-generation AR antagonist treatment (and withdrawal) and up to two previous chemotherapy regimens; had Eastern Cooperative Oncology Group performance status of 0/1; and had not received previous therapy with enzalutamide or an investigational AR antagonist.

### 2.2. Ethics

This extension trial was approved by the investigational review board or independent ethics committee of each participating centre. It was conducted according to the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. All patients provided written informed consent.

### 2.3. Treatment

In the phase 1/2 ARADES trial, patients were randomly assigned to receive ODM-201 at doses between 200 and 1800 mg daily (phase 1) and stratified by previous chemotherapy and treatment with CYP17i, and to receive expanded dose levels of 200, 400, and 1400 mg daily (phase 2) [14]. We report here the safety and efficacy results for ARADES patients with extended follow-up who were CYP17i- and chemotherapy-naïve or CYP17i-naïve and chemotherapy-pretreated. All patients received oral ODM-201 at doses between 100 and 900 mg twice daily, with each patient's treatment dose being the same dose that the patient received at week 12 [14]. Patients were permitted one dose increase to the highest tolerated dose identified as safe, but not beyond the highest phase 2 dose, and visited the study centre monthly for 6 mo, followed by visits at 3-monthly intervals.

### 2.4. Antitumour activity assessment

Patients considered to have a complete response, partial response, or stable disease continued treatment in the ARADES trial until disease progression (time to confirmed radiographic and/or to PSA progression, as defined by the Prostate Cancer Working Group 2, PCWG2 [15]) or until they experienced an intolerable AE.

Soft tissue response was assessed via computed tomography/magnetic resonance imaging of the chest, abdomen and pelvis during the last visit (before discontinuation or data cutoff). Changes in target lesions were evaluated according to Response Evaluation Criteria in Solid Tumors 1.1. Responses were assessed as complete response, partial response, stable disease, progressive disease or not evaluable, stratified by dose and treatment group. Patients with confirmed responses for $\geq$6 mo were classified as durable responders. Changes in bone lesions were assessed during the last visit and reported as improvement, stable/no change, or progression by the investigator according to PCWG2 criteria.

Clinical disease progression was determined by the investigator and included loss of appetite/weight, change in bone pain/worsening bone pain, increased use of analgesics, cachexia/decrease in performance scale and other symptoms of progressive CRPC.

### 2.5. Safety and tolerability

AEs were classified 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 (version 4.03). Electrocardiograms (ECGs) and laboratory assessments (haematology, serum chemistry, hormones and urine tests) were performed.

The initial analysis of this trial used a data cutoff of October 2013 [14]; safety data for patients still receiving the study drug at this time were collected through to October 2014 and contributed to the extended safety analysis.

### 2.6. Statistical analysis

Analyses of antitumour activity and safety were performed for patients who received at least one dose of ODM-201. The Kaplan-Meier method was used for time-to-progression analyses, with results reported as the median values with associated 95% confidence intervals (CIs) and interquartile ranges (IQRs). The Cox proportional hazards model was used to estimate hazard ratios (HRs) and associated 95% CIs. The log-rank test was used to compare the median treatment duration between patient subgroups. All safety data were summarised using descriptive statistics.

## 3. Results

### 3.1. Patients

A total of 77 patients with CYP17i-naïve CRPC had extended follow-up during the ARADES trial and contributed to this safety analysis; all received at least one dose of ODM-201 (safety population). Of the study cohort, 42 patients (54.5%) were chemotherapy-naïve and 35 (45.5%) received prior chemotherapy. Baseline demographic and clinical characteristics are shown in Table 1.

The most common reason for discontinuation was disease progression (84.4% of patients), with five patients (6.5%) discontinuing due to AEs and one patient withdrawing consent. The median duration of ODM-201 treatment for all patients was 8.2 mo (95% CI 5.6–11.0; IQR 2.8–13.5); this was longer for the chemotherapy-naïve subgroup (9.3 mo, 95% CI 6.9–13.0, IQR 4.1–15.8) than for chemotherapy-pretreated patients (6.0 mo, 95% CI 2.9–8.4, IQR 2.8–11.7; log-rank $p = 0.0135$). The median follow-up time (from the start of study treatment to the end-of-study visit) was 9.2 mo (95% CI 6.8–12.0, IQR 3.7–14.8). Four patients (5.2%) continued treatment on a named patient (compassionate) use basis after they discontinued the study; the shortest duration of compassionate use (from the time of study discontinuation) was 9 mo, and the longest was 22 mo. Combining the compassionate use time with the on-study treatment time for these four patients resulted in a total on-treatment time of 31 mo (minimum) to 53 mo (maximum). One patient continued to take ODM-201 on compassionate basis until November 2016, rendering analysis incomplete for these patients. Overall, the longest follow-up time, excluding compassionate use, was 35.4 mo.

### 3.2. Safety

At least one AE was experienced by 75 patients (97.4%), but the majority (61.1%) were grade 1; only 24 patients (31.2%) reported grade ≥3 AEs, including one patient with grade 4 lymphoedema and two patients who died with grade 5 AEs (one staphylococcal infection and one PCa). The most common grade 3 AE was anaemia, which occurred in four patients (5.2%), while the most common AE of any grade was fatigue/asthenia, reported by 27 patients (35.1%). Grade 3 fatigue/asthenia occurred in only two patients (2.6%), and no higher-grade fatigue/asthenia events were reported. A similar pattern of AEs was seen in each patient subgroup and no dose-related trends were observed. Only one reported AE (grade 2 fatigue) led to discontinuation and was thought to be related to ODM-201. No dose reductions were required throughout the study. The incidence of AEs reported by CYP17i-naïve patients during this extended follow-up was similar to that reported by the same patient group during the main ARADES trial at the time of the original cutoff date (October 3, 2013): fatigue/asthenia was the most common AE of any grade (23 patients, 29.9%) and grade 3 fatigue/asthenia was reported by two patients (2.6%). Furthermore, during the phase 1/2 of ARADES, the most common grade 3 AEs were anaemia and pain, reported by three patients (3.9%), and only one patient (1.3%) had a grade 4 AE (lymphoedema).

Treatment-related AEs (TRAEs) occurred in 27 patients (35.1%) and are listed in Table 2. The majority of TRAEs (63/64, 98.4%) were grade 1/2 in severity, with grade 1 occurring in 25 patients (32.5%). Two patients had single grade 2 TRAEs (asthenia and hot flush) and one patient experienced a grade 3 fatigue event. The most common TRAEs

**Table 1 – Patient demographics and clinical characteristics for the safety population (all doses 100–900 mg twice daily) in the extension study.**

| | Total |
|---|---|
| Patients (*n*) | 77 |
| Age, yr (range) | 69 (53–83) |
| Median prostate-specific antigen, mg/ml (range) | 94 (3–1294) |
| Measurable disease, *n* (%) | 32 (41.6) |
| **Change in soft tissue disease** [a] | |
| Disease progression at screening, *n* (%) | |
| Prostate-specific antigen rise only | 18 (23.4) |
| Radiographic with a rise in prostate-specific antigen | 55 (71.4) |
| Radiographic without a rise in prostate-specific antigen | 4 (5.2) |
| Disease localisation at screening, *n* (%) | |
| Bone only | 29 (37.7) |
| Soft tissue only | 13 (16.9) |
| Bone and soft tissue | 34 (44.2) |
| None | 1 (1.3) |
| Soft tissue disease metastasis site at screening, *n* (%) | |
| No metastases | 30 (39.0) |
| Visceral [b] | 7 (9.1) |
| Other | 35 (45.5) |
| Visceral [b] and other | 5 (6.5) |
| Bone metastases at screening, *n* (%) | 63 (81.8) |
| Circulating tumour cells (≥5 cells/7.5 ml of blood), *n* (%) | 32 (41.6) |
| Number of previous chemotherapy regimens, *n* (%) | |
| 0 | 42 (54.5) |
| 1 | 30 (39.0) |
| 2 | 5 (6.5) |

[a] Assessed using Response Evaluation Criteria in Solid Tumors criteria.
[b] Visceral included metastases in one or more of the following organs: liver, lung, kidney.

**Table 2 – Treatment-related adverse events (AEs) occurring in more than one patient for the safety population (all doses 100–900 mg twice daily) in the extension study until the end-of-study visit or the data cutoff date.**

| | Treatment-related AEs, *n* (%) | | | | |
|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4/5 | Total (*n* = 77) |
| Any treatment-related AE | 25 (32.5) | 8 (10.4) | 1 (1.3) | 0 (0.0) | 27 (35.1) |
| Common treatment-related AE | | | | | |
| Fatigue/asthenia | 6 (7.8) | 4 (5.2) | 1 (1.3) | 0 (0.0) | 8 (10.4) |
| Decreased appetite | 4 (5.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (5.2) |
| Diarrhoea | 4 (5.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (5.2) |
| Hot flush | 2 (2.6) | 1 (1.3) | 0 (0.0) | 0 (0.0) | 3 (3.9) |
| Arthralgia | 1 (1.3) | 2 (2.6) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Back pain | 1 (1.3) | 2 (2.6) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Constipation | 2 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Flatulence | 2 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Gynaecomastia | 2 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Headache | 2 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Myalgia | 2 (2.6) | 1 (1.3) | 0 (0.0) | 0 (0.0) | 2 (2.6) |
| Nausea | 1 (1.3) | 1 (1.3) | 0 (0.0) | 0 (0.0) | 2 (2.6) |

were fatigue/asthenia, reported by eight patients (10.4%); diarrhoea and decreased appetite, reported by four patients (5.2%) for each; and hot flush, reported by three patients (3.9%).

There was no relevant change in the frequency of the most common TRAEs over study duration, as demonstrated by the evaluation of these AEs within 1 and 2 yr of the patients' first dose (Table 3). Only two TRAEs were captured during the second year of treatment (one new event of constipation and one recurring hot flush, both grade 1). In addition, no clinically significant changes in laboratory tests, vital signs, or ECG parameters were observed over the extended study period.

### 3.3. *Antitumour activity*

PSA analyses included 76 CYP17i-naïve patients who had evaluable data. The majority of patients responded to ODM-201 treatment at all doses tested, as shown in terms of the maximum reduction of PSA from baseline (Fig. 1A). Responder rates (maximum PSA change of ≥50%) were 68.3% for chemotherapy-naïve (*n* = 28/41) and 42.9% for chemotherapy-pretreated (*n* = 15/35) patients. This is further illustrated by plots of PSA concentration changes from baseline over time by patient in Fig. 1B.

Patients' last responses (before discontinuation or cutoff) in soft tissue and bone lesions and clinical progression were assessed in the safety population. Soft tissue responses for evaluable patients (*n* = 48) included one patient with a complete response (receiving 200 mg/d of ODM-201), seven patients with a partial response, and 16 with stable disease, whereas 24 patients experienced progressive disease. Most of the patients with progressive disease had received the lower ODM-201 doses (200 mg/d, *n* = 6; 400 mg/d, *n* = 13). Fig. 2 shows all patients (*n* = 13) who had either a complete or partial response throughout the study, with six patients classified as durable responders.

No new bone lesions were detected in the majority of patients (*n* = 45, 58.4%); bone lesions were classified as stable/no change in 48 patients (62.3%), and 25 patients (32.5%) had progressed. Overall, 22 patients (28.6%) experienced clinical progression; the most common clinical symptoms demonstrating clinical progression were worsening of pain/increased use of analgesics (17 patients, 41.5%).

Time-to-progression analyses included all CYP17i-naïve patients who started the main study treatment (*n* = 77); one patient was excluded for time to PSA progression (≥25% and ≥5 ng/ml increase from baseline) analyses (*n* = 76 evaluable patients). At the end of the study, the antitumour activity of ODM-201 (all doses) was demonstrated in both subgroups. The median time to PSA progression was 25.2 mo (95% CI 11.2–25.2, IQR 6.5–25.2) for all patients, 25.2 mo (95% CI 11.3–25.2, IQR 11.0–25.2) for chemotherapy-naïve patients, and was not reached (NR) for chemotherapy-pretreated patients (95% CI 5.5–NR, IQR 4.7–NR; Fig. 3A). The HR for PSA progression was 0.55 (95% CI 0.23–1.33; *p* = 0.1854) for chemotherapy-naïve compared with chemotherapy-pretreated patients, suggesting that although there were no statistically significant differences between treatment groups, there was a trend for improved antitumour activity among chemotherapy-naïve patients. The median time to radiographic progression was longer in the chemotherapy-naïve than in the chemotherapy-pretreated group (14.0 mo, 95% CI 8.1–33.3, IQR 5.6–33.3 vs 7.2 mo, 95% CI 2.7–11.0, IQR 2.6–11.6; HR 0.41, 95% CI 0.22–0.79; *p* = 0.0073; Fig. 3B).

For patients receiving expanded ODM-201 dose levels (*n* = 68; 200, 400 and 1400 mg/d), the HR for PSA progression was 0.47 (95% CI 0.12–1.82; *p* = 0.2743) for the

**Table 3 – Treatment-related adverse events (AEs) reported by the safety population (*n* = 77) within 1 and 2 yr of the first dose.** [a]

| | Patients reporting treatment-related AEs, *n* (%) | |
|---|---|---|
| | Within 1 yr | Within 2 yr |
| Any treatment-related AE [b] | 26 (34) | 27 (35) |
| Fatigue | 8 (10.4) | 8 (10.4) |
| Decreased appetite | 4 (5.2) | 4 (5.2) |
| Diarrhoea | 4 (5.2) | 4 (5.2) |

[a] Patient numbers: *n* = 77 for 0–1 yr and *n* = 28 for 1–2 yr.
[b] Events listed are those reported by ≥5% of patients for at least one time point.

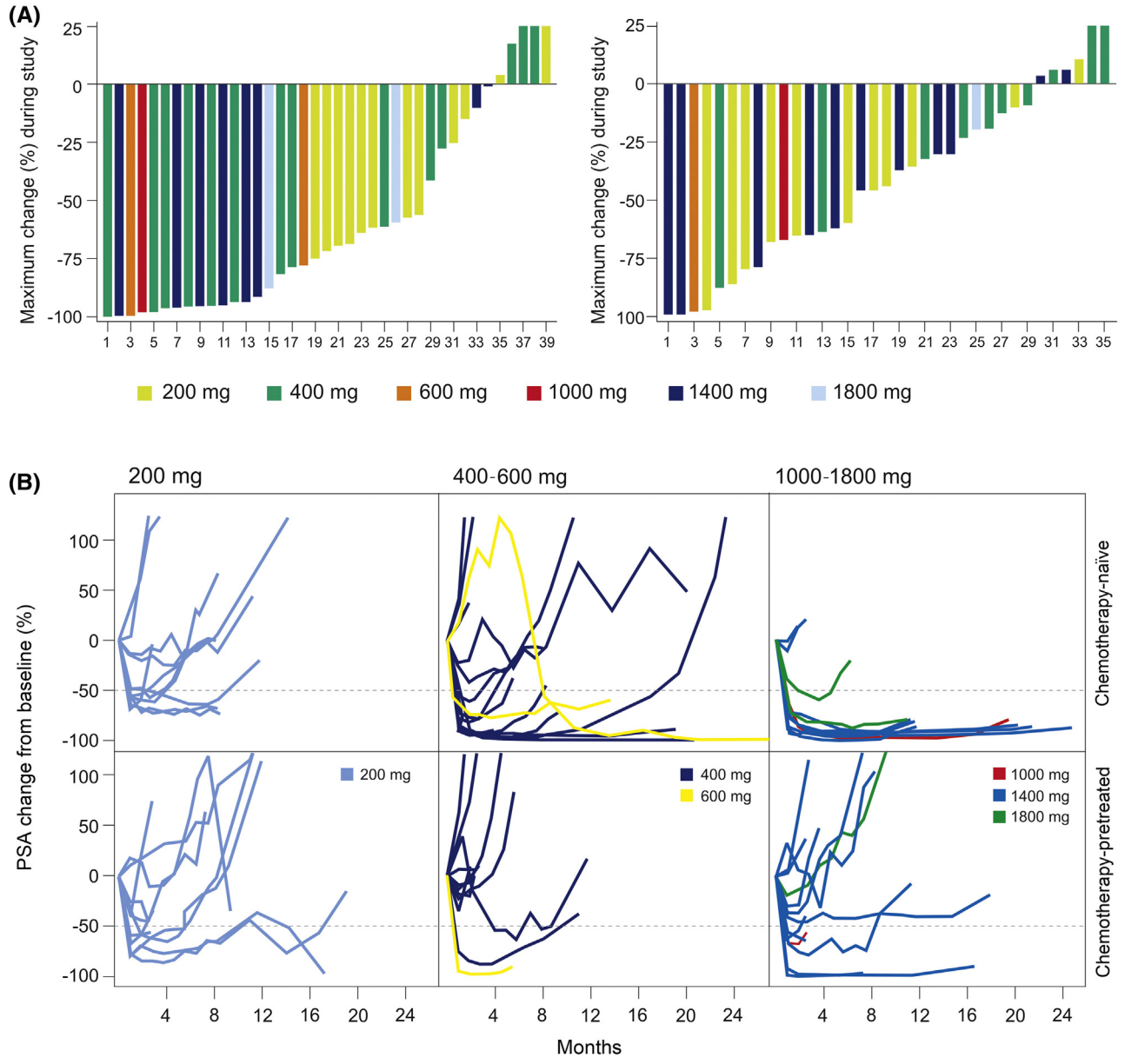


**Fig. 1 – (A) Maximum prostate-specific antigen (PSA) change by prior treatment group and dose level. Left: chemotherapy-naïve, CYP17 inhibitor–naïve patients (2 patients had no post-baseline data and therefore were considered as nonresponders; not shown). Right: chemotherapy-pretreated, CYP17 inhibitor–naïve patients. (B) PSA changes over time by patient, grouped by dose level.**

1400 mg/d group and 1.32 (95% CI 0.48–3.62; $p = 0.596$) for the 400 mg/d group when compared with the 200 mg/d group. The median time to PSA progression was NR for the groups receiving 200 and 1400 mg/d of ODM-201, and was 25.2 mo (95% CI 4.7–25.2, IQR 4.7–25.2) for patients receiving 400 mg/d.

## 4. Discussion

Extended follow-up for the ARADES trial showed that continued ODM-201 treatment was effective and well tolerated for up to 35.4 mo at all doses tested. This favourable safety profile reflects that seen in the analysis of 12-wk data [14], with the majority of AEs being mild and not considered related to treatment. The overall pattern of tolerability observed during extended ODM-201 therapy was appropriate for the treatment of CRPC, which typically occurs in an older population [16] in which anticancer treatment–related side effects can be poorly tolerated [17]. Many patients receiving AR-directed therapy are likely to have multiple comorbidities and be taking several concomitant medications. In fact, concerns regarding tolerability are a major factor contributing to the low use of chemotherapy among older men with PCa [18], while first-generation androgen deprivation therapy may be associated with an

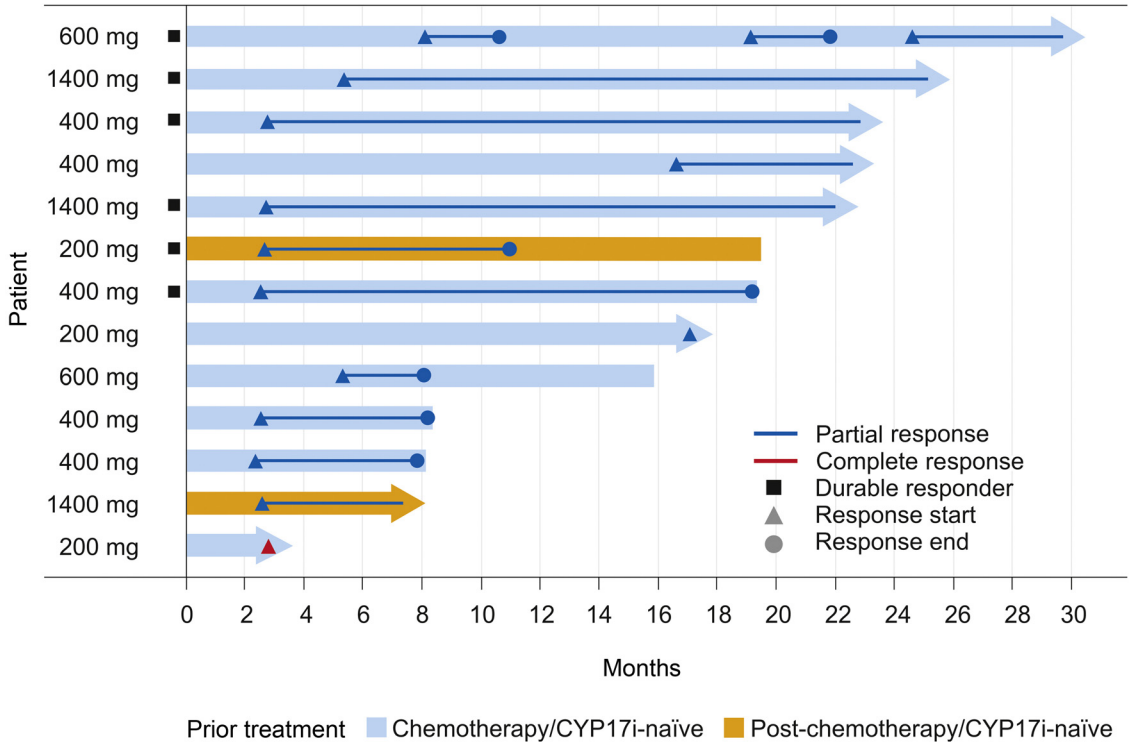


**Fig. 2 – Swimmer plot of patients' responses ($n$ = 13) according to Response Evaluation Criteria in Solid Tumors. Each bar represents one patient and indicates the duration of study treatment (mo). A right arrow cap indicates continued response (patient's response [partial response or complete response] at the last visit, before discontinuation). A durable responder is a patient who has a confirmed response for at least 183 d (6 mo).**

increased rate of cardiac events [19] and cognitive impairments [20].

The safety profile of extended ODM-201 dosing is typical for patients with advanced PCa and is in line with that reported for other second-generation AR antagonists, such as apalutamide [21], enzalutamide [22–25], and abiraterone acetate [26,27], with low incidence of fatigue/asthenia, the most common AE associated with AR antagonist treatment. Furthermore, the frequency of AEs during this extension trial is comparable to the incidence reported in the main ARADES trial for this patient population. Fatigue/asthenia of any grade was the most common AE, occurring in 30–35% of patients, and the overall number of discontinuations was also similar (2–6.5%), highlighting that extended exposure to ODM-201 does not cause any additional safety concerns.

As well as a favourable safety profile, prolonged treatment with ODM-201 led to continued disease suppression throughout the trial at all dose levels and in all subpopulations (Fig. 1). Radiographic assessment further supported the antitumour activity of extended ODM-201 dosing (Fig. 2); for example, the majority of patients (62%) had no bone metastases progression, similar to the bone scan assessment data reported for CYP17i-naïve patients in the main ARADES trial [14].

As expected, chemotherapy-naïve patients tended to respond better to treatment, and the higher doses (eg, 1400 mg/d) appeared to provide the best PSA suppression in these patients, in line with the analysis of the 12-wk efficacy data (86% PSA response in chemotherapy-naïve patients) [14]. The sustained PSA reductions and 14-mo time to radiographic progression observed here for chemotherapy-naïve patients are also consistent with the ARAFOR trial, in which the median time to radiographic progression was 15 mo (daily dose of 1200 mg) [28].

Although a trend towards a dose-dependent efficacy response was observed, there were no dose-related toxicities, in line with results from the phase 1/2 of the ARADES trial [14]. Previous pharmacokinetic analyses showed a dose-dependent, linear increase in ODM-201 exposure in patients receiving up to 1400 mg/d, but no further increase with ODM-201 doses $\geq$1800 mg/d, suggesting that the toxicity profile of this compound is not related to its pharmacokinetic profile [14].

Emphasising the tolerability and efficacy of ODM-201, one patient continued treatment on a named patient (compassionate) use programme until November 2016 and benefited from the treatment. Furthermore, four patients remained on treatment for a total of 31–53 mo, rendering safety analysis incomplete for these patients.

The main limitations of this study were the open-label, non-randomised study design [14], the relatively small number of patients included in the extended follow-up analyses, and the bias inherent in any follow-up trial. Any patient remaining on treatment at the end of the study will have already demonstrated tolerability for the agent over time. These responders are typically patients who benefited from androgen deprivation therapy over a long period before developing CRPC [29]. The absence of quality-of-life

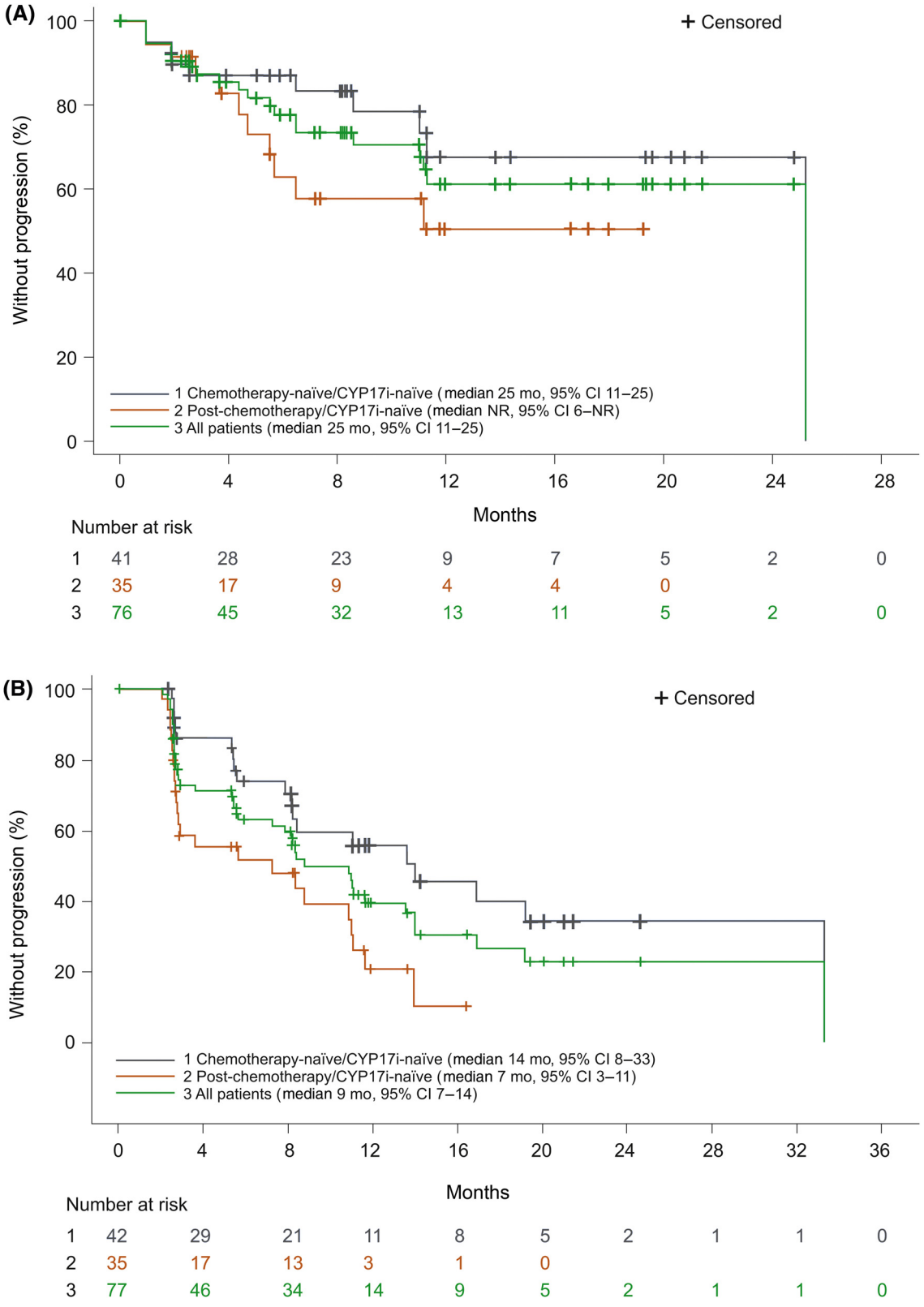


**Fig. 3 – Kaplan-Meier plots showing time to (A) prostate-specific antigen progression and (B) radiographic progression. CYP17i = CYP17 inhibitor; CI = confidence interval; NR = not reached.**

(QoL) measurements is a major limitation of this study, as cognitive impairments have been associated with AR therapy [19,20]. Future trials evaluating the impact of prolonged ODM-201 treatment on QoL and cognitive functions are needed and could potentially differentiate ODM-201 from other treatment options for CRPC.

Overall, the favourable safety and efficacy observed during this extended follow-up support further evaluation of ODM-201 in placebo-controlled phase 3 trials. In the ARAMIS trial (NCT02200614), metastases-free survival is being evaluated in patients with nonmetastatic CRPC receiving ODM-201 [30]. In the ARASENS trial (NCT02799602), the overall survival of ODM-201–treated patients with metastatic castration-sensitive PCa will be assessed.

## 5. Conclusions

Extended exposure to ODM-201 is well tolerated, with no additional safety concerns. This safety profile coupled with clinical activity and sustained disease suppression indicates that ODM-201 may represent a new treatment option for patients with CRPC.

***Author contributions:*** Karim Fizazi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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*Drafting of the manuscript:* Fizazi, Mustonen.
*Critical revision of the manuscript for important intellectual content:* Fizazi, Massard, Bono, Kataja, James, Tammela, Joensuu, Mustonen, Aspegren.
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