Darolutamide in hormone-sensitive and castration-resistant prostate cancer

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Introduction

Worldwide, prostate cancer accounts for 7.1% of total new cancer diagnoses and 3.8% of total cancer deaths in 2018. It is the 2nd most frequent cancer and the 5th leading cause of cancer death in men [1]. Androgen deprivation therapy (ADT) is the treatment cornerstone for prostate cancer at both metastatic and locally advanced stages [2,3]. For the latter, despite castration levels of testosterone (<50ng/ml), it may be observed a biochemical progression of the disease, with a rise in prostate specific antigen (PSA) without any evidence of metastasis using conventional imaging instruments [4]. This condition is defined as non-metastatic castration-resistant prostate cancer (nmCRPC). Without treatment, the median bone-metastasis free survival ranges from 25 to 30 months. Baseline PSA and PSA velocity are independent predictors of time to first bone metastasis, overall survival (OS) and bone-metastasis free survival in patients with nmCRPC [5,6]. Three randomized placebo-controlled clinical trials evaluated the efficacy of three different androgen-receptor (AR) inhibitors: enzalutamide (PROSPER) [7,10], apalutamide (SPARTAN) [8,11] and darolutamide (ARAMIS) [9,12] in patients diagnosed with nmCRPC. All three studies demonstrated an advantage in terms ofmetastasis-free survival (MFS) -primary endpoint - and OS – at longer follow up [7-12].

Resistance to castration treatment frequently occurs due to different genetic alterations of the AR such as amplification, mutation and splice variant [13]. While W741L mutation has shown to determine resistance to bicalutamide [14], T877A mutation is associated with flutamide resistance [15] whereas F876L mutation can lead both bicalutamide and apalutamide to act as agonists [16]. Darolutamide is a novel androgen receptor (AR) inhibitorable to overcome resistance of AR-targeted treatments andinhibit over-expressed or mutated receptors [13].

Introduction to darolutamide

Chemistry

Darolutamide (ODM-201) is a nonsteroidal androgen receptor antagonist. It is composed of a mixture (1: 1) of two pharmacologically active diastereomers (ORM-16497 and ORM-16555), structurally different from other second-generation antiandrogens [13, 17].,with keto-darolutamide (ORM-15341) the pharmacologically active metabolite.

Mechanism of action

ODM-201 directly binds with high affinity to the ligand-binding domain of the AR and competitively inhibits androgen binding as well as AR nuclear translocation and AR-mediated transcription [18].

Pharmacodynamics

Darolutamide and its main metabolite have a significantly lower inhibition constant (Ki) (11 and 8 nM, respectively) compared to enzalutamide and apalutamide in a competitive AR binding assay. When tested on human embryonic kidney 293 cells (HEK293) expressing AR, their inhibitory concentrations (IC50) were lower than other second-generation antiandrogens levels (26 and 38 nM, respectively), demonstrating greater efficacy in AR inhibition[13].

In vitro tests showed that darolutamide and its main active metabolite act as antagonists even in the presence of AR mutations (F876L, W741L and T877A) which confer resistance to other first and second-generation antiandrogens [13].

Although primarily located in the cytoplasm, ARs migrate to the nucleus in presence of testosterone for gene transcription acivation [19]. Bicalutamide is unable to block the testosterone-mediated nuclear translocation of ARs overexpressed, unlike enzalutamide, apalutamide, darolutamide and its metabolite, [13].

Antiandrogens block the negative hypothalamic-pituitary-gonadal feedback which, in turn, inhibits the release of luteinizing hormone-releasing hormone (LH-RH) in presence of testosterone: as a result, serum testosterone level increases, and competes for ARs binding [17]. In *invivo* test, darolutamide has reported poor permeability through the blood-brain barrier (BBB), with a significantly lower brain/serum ratio than enzalutamide and darolutamide (1.9%-3.9%, 27% and 62%, respectively), no consequent substantial effect on the hypothalamic-pituitary-gonadal axis [13] anda lower risk of seizures. In a castration-resistant prostate cancer (CRPC) mouse model, darolutamide did not increase testosterone levels and significantly inhibited tumour growth compared to enzalutamide [13]. When tested on cell lines derived from bone metastases of CRPC patients (VCaP cell) with overexpressed AR, in presence of a synthetic androgen (mibolerone), ODM-201 and ORM-15341 have been shown to suppress androgen-induced proliferation more effectively than enzalutamide and apalutamide.

Pharmacokinetics

The pharmacokinetic aspects of darolutamide were evaluated in the phase 1-2 ARADES trial (NCT01317641 and NCT01429064) which recruited individuals with progressive metastatic castration-resistant prostate cancer (mCRPC). This drug was rapidly absorbed when orally administered and reached its maximum plasma concentration in 3.0-5.1 hours (median t_{max} on day 1 for ORM-15341: 1.5 - 5.0 h). The steady-state of plasma concentrations was reached after one week of continuous treatment. At steady state, drug exposure (AUC_t and C_{max}) apparently increases in a linear fashion with dose escalation up to 1400 mg whereasthe exposure does not increase at following administrations (up to 1800 mg), achieving a plateau. The average half-lives ($t_{½}$) of darolutamide and its main active metabolite at steady state are 15.8 h and 10.0 h, respectively, regardless of dose (200-1800 mg) [20].

In the ARADES trial, darolutamide was administered as oral 100 mg capsules. In the phase 1 trial ARAFOR (NCT01784757), which recruited chemotherapy-naive mCRPC patients, the pharmacokinetic profile of two tablet products (TabA, TabB) were evaluated against capsules and effect of food on the absorption of darolutamide when administered as tablets[21]. The study showed that the ratio of the area under concentration versustime curve (AUC_{0-48}) between capsules and the two tablet products were approximately equal to the single unity ($AUC_{0–48}$ capsules/TabA ratio: 1.06; $AUC_{0–48}$ capsules/TabB ratio: 0.97). A similar result was observed for the C_{max} ratio (1.16 for capsules/Tab A ratio, 1.00 for capsules/TabB). Comparing the administration of the tablets under fasting conditions or 30 minutes after a standard high calorie high fat meal, it was found that absorption is slower with food but C_{max} and AUC reported two-fold increase; the same trend was observed for its main metabolite. No significant difference in terms of ORM-15341 / ODM-201 ratio was observed between capsules and tablets (C_{max}: 1.5–1.8; AUC: 1.4–1.7) [21].

When administered intravenously, the apparent volume of distribution of darolutamide is 119 L and the clearance (% CV) is 116 mL/min (39.7%). The plasma protein binding of ODM-201 and ORM-15341 is 92% and 99.8%, respectively [18].

Darolutamide is mainly metabolised by cytochrome P450 3A4 (CYP3A4) (approximately 30%); to a lesser extent, to the metabolism of darolutamide is provided by CYP1A1, Aldo-Keto Reductase 1C3, alcohol dehydrogenase, carbonyl reductase, O-glucuronidation, mainly mediated by the Uridine 5'-diphospho-glucuronosyltransferase (UGT)1A9 [22]. *In vitro,* darolutamide has no or minimal inhibitory effect on nine CYP isoforms; however, darolutamide and its diastomers have shown to be moderate to strong inducers of CYP3A4 enzyme activity, while keto-doralutamide to be a weak to moderate inducer of CYP3A4 [22]. Several *in vitro* tests have shown that darolutamide is a substrate of two drug efflux proteins: the breast cancer resistance protein (BCRP) and theP-glycoprotein (P-gp) with P-gp

saturation at test concentration (<10 µM)far below the clinically relevant concentrations of darolutamide [22].

In phase 1 trial, the concomitant administration of a CYP3A4, P-gp and a BCRP inhibitor (itraconazole) resulted in an increased darolutamide exposure (1.7-fold), which is less than the ≥ 5-fold increase when a sensitive CYP3A4 substrate (e.g. midazolam, lovastatin) is co-administered with a potent CYP3A4 inhibitor [22]. Co-administration of a CYP3A4 and a P-gp inducer (rifampicin) resulted in a 72% decrease in darolutamide exposure, although this drug and other CYP inducers are rarely included in polypharmacy of patients with prostate cancer [22, 23].

In 15 healthy male volunteers of a phase 1 study, darolutamide demonstrated only minimal CYP induction and no P-gp inhibition effects, when administered concomitantly with two substrates, midazolam and dabigatran etexilate, respectively [22]. Preclinical studies have shown that darolutamide can inhibit BCRP transporters, organic anion transporter (OAT) 3, organic anion transporter polypeptide (OATP) 1B1 and OATP 1B3, with the latter the substrate of rosuvastatin [22]. In a phase 1 study, the effect of darolutamide on rosuvastatin was investigated in 30 healthy patients: the plasma $AUC_{0\text{-}24}$ and C_{max} of rosuvastatin were approximately five times higher when administered with darolutamide over rosuvastatin alone; nonetheless, rosuvastatin t_{max} and $t_{½}$ did not vary, underlying no alteration of total plasma clearance . No increase in adverse events was recorded [22].

In a post hoc analysis of the double-blind, placebo-controlled phase 3 clinical trialARAMIS (NCT02200614), the effect of concomitant drugs on the pharmacokinetics of darolutamide as weel as the impact of concomitant use of statins on patient safety were evaluated [23]. No significant effect on darolutamide pharmacokinetics was observed from the concomitant use of other drugs such as antihypertensives, anticoagulants, analgesics, , proton pump inhibitors, antidepressants, anxiolytics and different treatments for urological and mental

disorders [23]. Furthermore, the incidence of adverse events (AEs) was similar between statin users and non-statin users for both darolutamide and placebo arms [23].

Darolutamide excretion is predominantly urinary: 63.4% is eliminated in urine while 32.4% in faeces after a single radiolabelled oral dose (7% and 30% unchanged, respectively) [18].

When tested on volunteers with severe renal impairment(estimated glomerular filtration rate (eGFR) of 15-29 mL/min / 1.73 m2), not under dialysis treatment or with moderate hepatic impairment (Child-Pugh Class B), the exposure to darolutamide increased by approximately 2, 5 and 1.9 times, respectively, when compared to healthy subjects. No data were found in patients with end-stage renal disease (eGFR <15 mL/min / 1.73 m2) or with severe hepatic impairment (Child-Pugh C) [18].

Clinical efficacy of darolutamide

The efficacy of darolutamide in prostate cancer was initially evaluated in phase 1-2 studies (Table 1). The ARADES trial was an open-label phase 1–2 trial that assessed safety, tolerability and efficacy of darolutamide withphase 1 consisting of a non-randomized dose-escalation cohort while phase 2 including a randomized dose-expansion cohort. During phase 1, the PSA response (defined as ≥ 50% decrease of in serum PSA from baseline) was achieved by 81% of patients at week 12. In phase 2, patients were randomly assigned to receive one of three daily doses of darolutamide (200 mg,400 mg, and 1400 mg). Within the phase 2 dose-expansion component, 11 patients (29%) from the 200 mg group,13 (33%) from the 400 mg group and 11 (33%) from the 1400 mg group had a PSA response at 12 weeks. Darolutamide activity was equally observed between all different doses administered. Stratifying patients into 3 groups according to previous regimens received (chemotherapy-naive and CYP17 inhibitor-naïve, post-chemotherapy and CYP17 inhibitor-naïve, post-CYP17 inhibitor), showed that the PSA response was significantly lower (7% in the 1400 mg group) in patients previously treated with CYP17 inhibitors than in those who

were naïve for both chemotherapy and CYP17 inhibitors (86% in the 1400 mg group), and those who previously received chemotherapy alone (36% in the 1400 mg group) [20].

In the open-label extension arm of the phase 1 ARAFOR trial, in which patients received twice daily 600 mg darolutamide in capsules with food, the PSA response rate was 83% (25 of 30 patients) at week 12; of these, 30% (9 of 30) had a ≥ 90% PSA reduction. The median time to PSA progression was 54 weeks (95% CI, 23–NR) whereas the median time to radiographic progression was 66 weeks (95% CI, 41–79) [21].

A phase 2 study (NCT02933801) is underway to evaluate the efficacy of darolutamide as maintenance therapy in mCRPC patients previously treated with novel hormonal agents, and no disease progression after taxane treatment . In the aforementioned trial, patients have been randomized 1:1 to receive twice daily either darolutamide 600 mg or placebo , both with best supportive care, until disease progression. The primary endpoint is radiographic progression-free survival (rPFS) at 12 weeks [24].

Several phase 2 studies are ongoing. The EORTC-1532-GUCG (NCT02972060) aims to evaluate the activity of darolutamide in metastatic hormone-sensitive prostate cancer (mHSPC) patients as alternative to LHRH analogues. The experimental arm consists of patients administered with darolutamide 1200 mg daily whereasADT is administered for those in the non-comparative control arm. The primary endpoint is the PSA response at 24 weeks (defined as an ≥ 80% PSA drop within the darolutamide study arm) [25].

In the ODENZA trial (NCT03314324), mCRPC patients have been randomized to receive either 12-week enzalutamide followed by 12-week darolutamide or 12-week darolutamide followed by 12-week enzalutamide. The primary endpoint is single-patient’s preference between darolutamide and enzalutamide after completion of second period of treatment [26].

Regarding localized disease, a phase 2 trial (INTREPId, NCT04025372) is currently investigating whether the novelhormonal therapy for the intermediate-risk prostate cancer is as effective as the standard hormone therapy, while preserving erectile function. Men will be randomized to receive either 6 months of gonadotropin-releasing hormone (GnRH) agonist plus bicalutamide 50 mg daily with radiotherapy (RT) or 6 months of darolutamide 600 mg twice daily with RT. The primary endpoint is PSA nadir ≤ 0.5 within 6 months from the end of treatment [27].

Among phase 3 studies, while the ARASENS trial (NCT02799602) is ongoing, preliminary results from ARAMIS trial have recently become available, (Table 2). In the ARAMIS trial, 1509 patients diagnosed with nmCRPC - according to conventional imaging including computerized tomography and bone scans - who had <10 months PSA doubling times (PSA-DT) and a minimum baseline PSA level of 2 ng/ml, were randomized to receive, in association with ADT, twice daily either darolutamide 300 mg or placebo. The primary endpoint was metastasis-free survival (MFS) while secondary endpoints were OS, time-to-pain progression, time-to-first symptomatic skeletal event and time-to-first cytotoxic chemotherapy. The median MFS was 40.4 months in the darolutamide group and 18.4 months in the placebo group (HR 0.41; 95% CI, 0.34 to 0.50; P<0.001). In terms of secondary endpoints, Darolutamide was associated with better outcomes when compared to placebo (Table 3) [9].

Survival data, conducted following 254 confirmed deaths, have recently been published from ARAMIS trial with15.5% deaths from darolutamide group and 19.1% from placebo group. Darolutamide has been associated with a statistically significant 31% reduction in the risk of death when compared to placebo [12].

At the European Urology Congress 2020, a subgroup analysis of the ARAMIS trial has been presented. Patients were stratified into two groups according to PSA-DT (≤6 months or >6

months) to assess the effect on efficacy and safety. Darolutamide reported a decreased risk of metastasis and death of 59% in the PSA-DT ≤6 months subgroup (HR 0.41; 95% CI 0.33-0.52) and 62% in the >6 months subgroup (HR 0.38; 95% CI 0.26-0.55), respectively. Furthermore, the 2 groups under investigation reported a similar safety profile [28].

In the context of metastatic hormone-sensitive prostate cancer (mHSPC), the ARASENS trial is ongoing. Approximately 1300 patients have been randomized to receive twice daily either darolutamide 600 mg plus ADT and docetaxel (6 cycles) or placebo plus ADT and docetaxel (6 cycles). The primary endpoint is the OS. Secondary endpoints include time to mCRPC, initiation of subsequent anticancer therapy, symptomatic skeletal event-free survival, time-to-first symptomatic skeletal event, first opioid use, pain progression, and deterioration of symptoms. The results of the ARASENS study are not yet available [29].

Safety and tolerability

Darolutamide was reported to be well tolerated in phase 1 and 2 studies. In the dose-escalation part of the ARADES trial, the vast majority ofAEs (93%) ranged from grade 1 to2 and primarily included fatigue or asthenia (42%). None of the reported grade 3–4 AEs was found to be related to darolutamide. Even in phase 2 of ARADES study the vast majority of AEs (91%) were categorised as grade 1–2. According to specialists' knowledge, AEs related to darolutamide were reported in 35% of patients, largely including fatigue or asthenia for 12% of patients [20].

In the ARAFOR trial 73% of patients reported AEs; of these, 91% were categorised as grade 1 or 2. The most common AEs were grade 1 fatigue in four patients (13%) and grade 1 to 3 nausea in four patients (13%). Darolutamide-related AEs – all grade 1 - were reported in 6 patients (20%) including fatigue, decreased appetite, headache, abdominal pain, solar dermatitis, tinnitus and dysgeusia [21].

Darolutamide showed a favourable toxicity profile also in the ARAMIS study. The incidence of AEs was similar between the experimental and placebo arms (83.2 % vs 76.9%, respectively) and a large number of AEs - 54.6% for darolutamide and 54.2% for placebo - were grade 1 or 2. The percentage of patients who discontinued darolutamide because of AEs was 8.9% versus 8.7% in the placebo group. All adverse events occurred in less than 10% of patients within both groups, except for fatigue. Regarding AEs generally associated with new antiandrogen therapy such as fractures, falls, seizures and weight loss, slight or no differences were observed between the darolutamide group and the placebo group. In particular, the incidence of seizures was 0.2% for both groups [9].

Noteworthy, evaluating the safety profile of ARAMISPROSPER and TITAN trials - in contrast to enzalutamide and apalutamide - darolutamide shows a similar incidence of seizures, dizziness, and cognitive impairment compared to placebo in ARAMIS trial (Table 4) [7,8].

Current state of darolutamide

Darolutamide is currently FDA approved in the nmCRPC setting from July 30, 2019. On the contrary, for the same setting, enzalutamide and apalutamide were approved on July 13, 2018 and February 14, 2018, respectively [2]. European guidelines advise on the use of apalutamide, darolutamide or enzalutamide for nmCRPC patients withhigh risk of disease progression (PSA-DT < 10 months) to prolong timetometastasis [3]. However, no indications are given about the preferred regimen between apalutamide, darolutamide and enzalutamide. Despite comparable efficacy, the different toxicity profile of the aforementioned regimens should be taken into consideration. Darolutamide has an unique profile among new androgen receptor-targeted agents (ARTA) with demonstrated low impacton clinically relevant drug interactions. The enzymatic activity of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4, assessed by means of standard substrates, was not affected - or only slightly inhibited - *in vitro* by darolutamide [22].

This may be important considering that prostate cancer mainly affects older individuals potentially exposed to polypharmacy.

As mentioned in the pharmacodynamics section, darolutamide has a low BBB penetration properties, unlike enzalutamide and apalutamide.*In vivo* animal model study was performed with 14C-labeled whole-body autoradiography comparing darolutamide versus enzalutamide. The results showed a 10-fold lower BBB penetration of [14] darolutamide compared with [14] enzalutamide [30].

This might be due to the similar incidence of seizures between experimental and control arms in ARAMIS trial. In agreement with this, we should consider the risk of falling and fracture for patients receiving new ARTA. This risk was evaluated in a systematic review and meta-analysis which showed12% incidence of all-grade falls associated with apalutamide, followed by enzalutamide (8%) and darolutamide (4.2%) [31].

On the other hand, unlike competitors, we currently have data on the use of darolutamide in the nmCRPC setting only. Consequently, the shortcoming could be the less experience of clinicians in handling this drug.

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Declaration of interest

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