The Current Landscape of Treatment in Non-Metastatic Castration-Resistant Prostate Cancer

Clinical Medicine Insights: Oncology
Volume 13: 1–5

DOI: 10.1177/1179554919833927

Joelle El-Amm[1] and Jeanny B Aragon-Ching[2]

[1]Hematology and Oncology, Lebanese American University, Beirut, Lebanon. [2]Genitourinary (GU) Medical Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA.

ABSTRACT: Non-metastatic castration-resistant prostate cancer (nmCRPC) is a heterogeneous disease with variable potential in developing into overt metastases. It is an area of increased unmet need in advanced prostate cancer and for which there had been no great treatments until recent US Food and Drug Administration (FDA) approval of 2 novel anti-androgens apalutamide and enzalutamide, which were both approved given benefit in metastasis-free survival. Early data on the use of darolutamide, another novel anti-androgen, are also explored. This review discusses the pivotal trials that led to the approval of apalutamide and enzalutamide in the nmCRPC setting and discusses the key promises and challenges with the use of these agents.

KEYWORDS: non-metastatic CRPC, apalutamide, enzalutamide, darolutamide, ODM-201, metastasis-free survival

RECEIVED: September 25, 2018. **ACCEPTED:** January 16, 2019.

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Jeanny B Aragon-Ching, Genitourinary (GU) Medical Oncology, Inova Schar Cancer Institute, 8505 Arlington Blvd., Suite 100, Fairfax, VA 22031, USA.
Email: Jeanny.Aragon-Ching@inova.org

Introduction

Prostate cancer is the second most common form of cancer in men in the United States representing 19% of newly diagnosed cancers and the third leading cause of cancer death responsible for an estimated 39 430 deaths in 2018.[1] While most of the early-stage prostate cancer is curable, a subset of men will progress with biochemical recurrence. Prostate cancer becomes a fatal metastatic disease by progressing first to non-metastatic castration-resistant prostate cancer (nmCRPC), which is defined as prostate-specific antigen (PSA) progression despite primary androgen deprivation therapy (ADT) in the absence of obvious disease obtained through conventional imaging.[2] Recently, there has been growing interest in treatment of nmCRPC in an attempt to delay progression to the metastatic state. The landscape of nmCRPC has recently rapidly changed with the advent of US Food and Drug Administration (FDA) approval for 2 anti-androgens, apalutamide and enzalutamide, both for delaying metastases. These novel androgen-modulating drugs holds promise for prolonging progression-free survival (PFS) and potentially ultimately, overall survival (OS).

Background on nmCRPC

The nmCRPC state is a "man-made" or artificial clinical state as CRPC arises from the use of ADT in men who present with biochemical recurrence of disease. Most patients who are diagnosed with biochemical recurrence have already undergone prior curative intent therapy with either radical prostatectomy or radiation therapy. As biochemical recurrence progresses, most patients will undergo chemical castration through the use of gonadotropin-releasing hormone receptor agonists or antagonists or by surgical castration. The average time to the development of castration resistance after starting hormonal deprivation in non-metastatic prostate cancer is 19 months.[3]

In the 1940s, Huggins and Hodges first showed that the effects of surgical orchiectomy could lead to prostate cancer regression.[4] Testosterone and the more potent dihydrotestosterone are the 2 main androgens that are responsible for the growth of the prostate by binding to the androgen receptor (AR). The AR plays a crucial role in the pathogenesis of the prostate cancer and its role remains important as a key therapeutic target even in the castration-resistant state. Androgen receptor antagonists work by competitively binding to the AR and blocking the binding of endogenous androgens and thus interrupting the androgen-dependent cellular cascade that leads to progression of prostate cancer. It is also customary practice to continue ADT despite development of castration resistance.[5] Retrospective data have shown a 2- to 6-month median survival advantage in patients with CRPC who had undergone orchiectomy compared with patients who were on luteinizing hormone-releasing hormone (LHRH) agonists, which were stopped when castration resistance developed.[6] Rat models have shown that in CRPC, some cancer cells remain androgen sensitive.[7] In addition, human autopsy studies have shown varying heterogeneity within prostate cancer cells with variable response to androgens.[8]

There has been a growing interest in the development of drugs that target the AR in nmCRPC; hence second-generation anti-androgens were developed. Second-generation anti-androgens have several advantages over the first generation ones. First, they have a higher affinity for the AR. Second, they do not have agonistic properties. Third, they inhibit the function of the AR by 3 mechanisms: prevention of binding of androgens to the AR, prevention of the translocation of AR to the nucleus, and prevention of binding of the AR to DNA.[9,10] While an in-depth discussion of the first-generation anti-androgens such as bicalutamide, nilutamide, and flutamide are

reviewed elsewhere and beyond the scope of this review,[11] given the above-mentioned limitations of these older generation anti-androgens, development and discovery of newer anti-androgens paved the way for increasing affinity to the AR and obviating the antagonist to agonist conversion as well as less efficient translocation of the AR to the nucleus.

The 3 second-generation anti-androgens, namely, enzalutamide (MDV3100), apalutamide (ARN-509), and darolutamide (ODM-201), have been the subjects of multiple recent clinical trials.

Until February 2018, there were no FDA-approved treatments for nmCRPC, and prior to the landmark clinical trials presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposiums (SPARTAN and PROSPER), these patients usually continued to receive ADT alone or had alternative hormonal therapies added or switched[12] and anti-androgen withdrawal if they were already on one.[13,14] Currently, men with nmCRPC who are at high risk of metastases have 2 treatment options: enzalutamide and apalutamide. However, the phase-III trial results involving darolutamide are expected soon. The following sections will review the pivotal trials that led to the approval of these agents.

Apalutamide (Formerly ARN-509)

Apalutamide is a synthetic biaryl thiohydantoin compound that was discovered with structure-activity relationship medicinal chemistry studies.[15] Apalutamide binds to the same ligand-binding site as bicalutamide but has a 7- to 10-fold higher affinity for the AR. Apalutamide has a similar mechanism of action to enzalutamide but has been shown to have greater anti-tumor activity than enzalutamide in a murine model.[16]

The first Phase II study for apalutamide was performed as a multicenter trial in men with high-risk nmCRPC (PSA ⩾ 9 ng/mL or a PSA doubling time ⩽10 months).[17] Patients in the study had no evidence of radiographical metastasis and presented with castrate levels of testosterone (⩽50 ng/dL). Primary outcome of the study was determination of a 12-week PSA response, and secondary outcomes were time to PSA progression (TTPP) and metastasis-free survival (MFS). At a median follow-up of 26.9 months, the median PSA reduction from baseline was 85%, with 89% of patients achieving a ⩾50% reduction in PSA. The median TTPP was 24 months, and at the time of analysis, the MFS was not reached.

SPARTAN Trial

SPARTAN (A Study of Apalutamide [ARN-509] in Men with Non-metastatic Castration-Resistant Prostate Cancer, ClinicalTrials.gov Identifier: NCT01946204) is a phase III trial comparing apalutamide with placebo that was the basis of the US FDA approval of apalutamide in February 2018 as the first treatment of nmCRPC.[18] SPARTAN was a prospective, randomized, double-blinded, placebo-controlled multicenter phase III trial, with 1207 patients at high risk of developing metastasis in nmCRPC patients who were randomized in a 2:1 fashion to either placebo with ADT or 240 mg/day apalutamide with ADT. A prostate-specific antigen doubling time (PSA-DT) of 10 months despite castrate levels of testosterone was defined as high risk of developing metastasis. The trial utilized conventional imaging scans to detect metastases with computed tomography (CT) scans of the chest, abdomen, and head as well as technetium scintigraphy bone scans at the time of study inclusion, and routine re-staging scans every 16 weeks. Patients who had pathologic lymph nodes that measured <2 cm in the pelvis at short axis were included. Further stratification and comparison to cN0 patients were made. Patients had to have at least a PSA of 2 ng/mL as an entry criterion for the trial. Furthermore, stratification for PSA-DT of >6 months vs 6 months and the additional use of bone-targeted agents was included. The primary endpoint of the trial was MFS, which was achieved with the apalutamide arm showing 40.5 months compared with 16.2 months for placebo (hazard ratio [HR]: 0.28, 95% confidence interval [CI]: 0.23-0.35; $P < .001$). All secondary endpoints differed significantly between the arms, favoring apalutamide. Other secondary endpoints such as time to symptomatic progression were also significantly improved in those who received apalutamide compared with those who received placebo with an HR of 0.45, 95% CI: 0.32-0.63, and $P < .001$.

However, several adverse events (AEs) of interest are noteworthy, including a higher incidence of rash that occurred in 23.8% of those who received apalutamide compared with only 5.5% in the placebo arm; hypothyroidism was found in 8.1% vs 2% in the placebo arm, as well as fracture occurring in 11.7% vs 6.5%. Study-wide, two cases of seizure were noted to occur. Regardless, given the primary efficacy trial results, apalutamide received FDA approval in the management of nmCRPC. There was no increase in the risk of serious AEs (24.8% vs 23.1%), but a higher risk of death (10 vs 1 patient) was observed in the study. These deaths occurred within 28 days of the last dose, and of the 10 patients in the apalutamide arm, prostate cancer was the attributable cause of death in 2 patients. However, non-cancer-related deaths occurred in others such as sepsis (n = 2), pneumonia (n = 1), multiple organ dysfunction (n = 1), and cardiovascular causes such as myocardial infarction (n = 2), cardiorespiratory arrest (n = 1), and cerebral hemorrhage (n = 1), while only 1 patient in the placebo arm had cardiorespiratory arrest as the cause of death. While considered an overall small number in terms of difference in death rates (1.2% vs 0.3% death in the apalutamide vs placebo arms, respectively), gains in benefit must be weighed against potential harms. A first survival analysis showed an HR of 0.7 (95% CI: 0.47-1.04, $P = .07$; median follow-up 20.3 months) for apalutamide, although longer follow-up is needed to answer whether there is an OS benefit with the use of apalutamide in nmCRPC.

Enzalutamide (Formerly MDV3100)

Enzalutamide is another second-generation AR antagonist; the safety and efficacy profile of which has been evaluated in 2 previously published placebo-controlled, multicenter phase III trials (AFFIRM and PREVAIL), which led to its approval in mCRPC in 2012.[19,20]

More recently, the STRIVE (Enzalutamide vs Bicalutamide in Castration-Resistant Prostate Cancer; ClinicalTrials.gov Identifier: NCT01664923) trial, a phase II randomized control trial, compared bicalutamide with enzalutamide in men with CRPC; 139 of whom had no evidence of metastatic disease.[21] In the nmCRPC group, median PFS was improved with enzalutamide compared with bicalutamide, at 8.6 months for bicalutamide vs not reached for enzalutamide, at an average follow-up of 17 months, specifically with an HR for radiographic progression or death, 0.24 (95% CI: 0.14-0.42). Overall, 87.8% of nmCRPC patients were free of radiological progression after 2 years of enzalutamide therapy.

PROSPER trial

The registration trial that evaluated enzalutamide's utility in the nmCRPC setting was called the PROSPER (Safety and Efficacy Study of Enzalutamide in Patients with Non-metastatic Castration-Resistant Prostate Cancer) trial. PROSPER was a phase III, double-blinded, randomized study that evaluated 1401 patients with nmCRPC randomized 2:1 to enzalutamide vs placebo.[22] Eligible men with nmCRPC, PSA doubling time ⩽10 months and PSA ⩾2 ng/mL at screening continued ADT and were randomized 2:1 to enzalutamide 160 mg or placebo. Randomization was stratified by PSA doubling time (<6 months vs ⩾6 months) and previous or current use of a bone-targeting agent at baseline. The primary endpoint was MFS. Secondary endpoints included TTPP, time to first use of new anti-neoplastic therapy, OS and safety. Enzalutamide significantly prolonged median MFS (36.6 months vs 14.7 months [$P<.0001$]), time to first use of new anti-neoplastic therapy (39.6 months vs 17.7 months [$P<.0001$]), and TTPP (37.2 months vs 3.9 months [$P<.0001$]) compared with placebo. In the first interim analysis of OS, there was a trend in favor of enzalutamide (HR = 0.80; $P=.1519$) though not statistically significant. Median duration of treatment was 18.4 months compared with 11.1 months for enzalutamide and placebo, respectively. Adverse events were higher with enzalutamide vs placebo (any grade: 87% vs 77%; grade ⩾3: 31% vs 23%; serious: 24% vs 18%). However, the discontinuation rates from either arm were similar: 10% with enzalutamide discontinued treatment due to AEs compared with 8% with placebo. The only AE of any grade occurring in >20% of the enzalutamide group was fatigue (33% vs 14% in placebo group). Adverse events of grade ⩾3 occurred in 31% of the enzalutamide group vs 23% of the placebo group, with the most common in the enzalutamide group being hypertension (5% vs 2%). Serious AEs occurred in 24% vs 18%. Adverse events led to study drug discontinuation in 9% vs 6%. Adverse events led to death in 3% vs 1%. Adverse events of special interest of any grade that occurred with ⩾2% greater frequency in the enzalutamide group were hypertension (12% vs 5%), major cardiovascular events (in 5% vs 3%), and mental impairment disorders (5% vs 2%). Three patients in the enzalutamide group had convulsions, all of which were considered to be serious and drug-related. One patient discontinued enzalutamide and another had complications that led to death. Falls and non-pathologic fractures occurred in 17% vs 8% of patients. The most common AEs leading to death were cardiac events, in 9 patients (1%) receiving enzalutamide and 2 (<1%) receiving placebo. These complications have important implications in the overall consideration of treatment of an asymptomatic population. Regardless, the trial was positive in delaying metastasis and improving MFS.

Based on the results of the PROSPER trial, the FDA approved on July 16, 2018 the use of enzalutamide in patients with nmCRPC with PSA-DT of 10 months (Table 1).

Darolutamide (ODM-201)

Darolutamide, formerly known as ODM-201, is a novel androgen-targeted signaling inhibitor. ODM-201 currently remains an investigational oral AR antagonist, which has a unique chemical structure with the purpose of androgen blockade and high affinity binding to the AR resulting in decreased growth of prostate cancer cells.[23-25] Pre-clinical studies showed that ODM-201 inhibits the AR more potently than other second-generation anti-androgens such as enzalutamide and apalutamide by increased anti-tumor activity compared with enzalutamide in a preclinical model of CRPC characterized by AR amplification and overexpression. Darolutamide has a similar mechanism of action to that of other second-generation anti-androgens but has additional ability to inhibit some mutant AR;[26] for instance, the F876L mutation, which arises as a result of enzalutamide or apalutamide use. Darolutamide also has a negligible ability to cross the blood-brain barrier, so it theoretically confers a much lower seizure risk than either enzalutamide or apalutamide. However, it has to be given as a twice-daily formulation.

ARADES/ARAFOR trials

There were initially 2 phase 1/2 trials that examined the pharmacokinetics and safety of ODM-201 called the ARADES and ARAFOR trials. ODM-201 showed promising anti-tumor activities and demonstrated tolerance in the subgroup of men presenting with mCRPC. The open-label multicenter, non-randomized, first-in-man, dose escalation phase 1 ARADES trial (clinicaltrials.gov NCT01429064) enrolled 24 patients, and anti-tumor activity was achieved at virtually all doses tested (200-1800 mg/day), and no dose-limiting

Table 1. Comparison of the second-generation androgen receptor antagonists for nmCRPC.

	APALUTAMIDE	ENZALUTAMIDE	DAROLUTAMIDE
Half-life	3-4 days	5.8 days	15.8 hours and 10 hours for metabolite
Status	FDA approved	FDA approved	Awaiting results
Metabolism	Hepatic	Hepatic	Hepatic
Dosage	240 mg po once daily	160 mg po once daily	600 mg po twice daily
Key phase III trial	SPARTAN	PROSPER	ARAMIS
N (patients)	1207	1401	1502
MFS vs placebo	40 months vs 14.7 months	36.6 months vs 13.6 months	Not available
Serious adverse events vs placebo (%)	25 vs 23	24 vs 18	Not available

Abbreviations: FDA, Food and Drug Administration; MFS: metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer.

toxicity was observed.[27] Further phase 2 extension trial enrolled 110 patients, which revealed that PSA decline was observed with all ODM-201 doses tested (200-1400 mg/day), and the 1400 mg/day dose led to the greatest PSA response in chemotherapy-naïve and CYP17 inhibitor (CYP17i)-naïve patients. Furthermore, ODM-201 was deemed to be safe, and most of the AEs reported only as grades 1 and 2. ARAFOR (clinicaltrials.gov NCT01784757) was an open-label multicenter trial that included a pharmacokinetic component (n = 30) and an open-label extension study (n = 30). Similarly, ODM-201 demonstrated a PSA response defined as a 50% decrease in PSA levels from baseline at week 12 in 25 out of 30 patients (83%) as the main efficacy result as well as very similar safety profile of 91% treatment-emergent AEs of grades 1 and 2 in this chemotherapy-naïve patient population.[28]

ARAMIS trial

The aforementioned trials suggested the benefit of moving ODM-201 forward in a large registration trial called the ARAMIS. The ARAMIS (clinicaltrials.gov NCT02200614) trial is a phase III randomized, multicenter, double-blind, placebo-controlled trial evaluating the safety and efficacy of darolutamide in patients with nmCRPC who are at a high risk of developing metastatic disease. The study sought to enroll 1508 patients who have now completed accrual. The primary endpoint of this study is MFS, defined as time between randomization and evidence of metastasis or death from any cause. The secondary objectives of this study are OS, time to first symptomatic skeletal event (SSE), time to initiation of first cytotoxic chemotherapy, time to pain progression, and characterization of the safety and tolerability of darolutamide. Results of the ARAMIS trial are projected to further elucidate the benefits of darolutamide in this nmCRPC setting, and while unavailable at the time of this writing, will be presented at the ASCO GU Cancers Symposium.

Sequencing and Implications in the Change of the Landscape of nmCRPC Treatment

The challenge of which agent to use first in a particular sequence remains unknown at this time. Given the array of options for the nmCRPC space, the ultimate decision rests on different variables including cost issues, preferences, availabilities, and side-effects. However, information regarding the PFS2 (second PFS or PFS with the first subsequent therapy that is defined as the time from randomization to investigator-assessed disease progression after first subsequent treatment for mCRPC or death) lends credence to the possibility of improvement in survival with the use of apalutamide that allows for subsequent use of abiraterone. In addition, emerging options with the use of more sensitive imaging may detect micrometastatic disease earlier, which could impact the use of these agents. Up to the time of FDA approval of these agents, the use of MFS as a registration trial has not been duly recognized by regulatory agencies as a surrogate endpoint for survival. While MFS has been retrospectively evaluated in different clinical states including that of localized disease[29] or biochemical recurrence,[30,31] it was not previously considered an acceptable surrogate for regulatory approval of denosumab, a RANK ligand inhibitor that was studied in a phase 3, double-blind, randomized, placebo-controlled trial in a similar population of nmCRPC patients in 2012.[32] However, the risk/benefit ratio was not deemed to favor use of denosumab given a modest 4-month median difference in the MFS over placebo. The studies utilizing apalutamide and enzalutamide have far exceeded those expectations with a delay in metastases of more than 2 years; hence, the FDA recognized that MFS is an objective and clinically meaningful measurable endpoint and conceivably balanced with an acceptable safety profile of a drug.[33] However, it remains to be seen if this would translate ultimately

to improvement in OS. In addition, more men would be subjected to the ongoing effects of anti-androgen therapy along with frailty, fractures, and central nervous system effects, which may not be trivial when taken for a long period of time. Whether the use of alternative agents such as darolutamide, which is touted to have less potential to cross the blood-brain barrier, has lesser potential central nervous system (CNS) effects also remains to be studied.

Conclusions

While there has not been a standard of care treatment for patients with nmCRPC for a long while, changes to the landscape of treatment was brought on by approval of both apalutamide and enzalutamide for those at highest risk for developing metastases. Continued research into the best agents, sequencing and implications of novel imaging would further clarify whether institution of earlier treatment clearly impacts ultimate OS.

Author Contributions

Wrote portions of the first draft of the manuscript: JE, JBAC; Contributed to the writing of the manuscript: JE, JBAC; Agree with manuscript results and conclusions: JE, JBAC; Jointly developed the structure and arguments for the paper: JE, JBAC; Made critical revisions and approved final version: JE, JBAC. All authors reviewed and approved of the final manuscript.

ORCID iD

Jeanny B Aragon-Ching https://orcid.org/0000-0002-6714-141X

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7–30.
2. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. *PLoS ONE*. 2015;10:e0139440.
3. Sharifi N, Dahut WL, Steinberg SM, et al. A retrospective study of the time to clinical endpoints for advanced prostate cancer. *BJU Int*. 2005;96:985–989.
4. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin*. 1972;22:232–240.
5. Virgo KS, Basch E, Loblaw DA, et al. Second-line hormonal therapy for men with chemotherapy-naive, castration-resistant prostate cancer: American Society of Clinical Oncology provisional clinical opinion. *J Clin Oncol*. 2017;35:1952–1964.
6. Taylor CD, Elson P, Trump DL. Importance of continued testicular suppression in hormone-refractory prostate cancer. *J Clin Oncol*. 1993;11:2167–2172.
7. Isaacs JT, Isaacs WB, Feitz WF, Scheres J. Establishment and characterization of seven Dunning rat prostatic cancer cell lines and their use in developing methods for predicting metastatic abilities of prostatic cancers. *Prostate*. 1986;9:261–281.
8. Shah RB, Mehra R, Chinnaiyan AM, et al. Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. *Cancer Res*. 2004;64:9209–9216.
9. Hu R, Dunn TA, Wei S, et al. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone refractory prostate cancer. *Cancer Res*. 2009;69:16–22.
10. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324:787–790.
11. Chen Y, Clegg NJ, Scher HI. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. *Lancet Oncol*. 2009;10:981–991.
12. Yokomizo Y, Kawahara T, Miyoshi Y, et al. Efficacy of immediate switching from bicalutamide to flutamide as second-line combined androgen blockade. *Biomed Res Int*. 2016;2016:4083183.
13. Kelly WK, Scher HI. Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. *J Urol*. 1993;149:607–609.
14. Scher HI, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. *J Clin Oncol*. 1993;11:1566–1572.
15. Jung ME, Ouk S, Yoo D, et al. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J Med Chem*. 2010;53:2779–2796.
16. Clegg NJ, Wongvipat J, Joseph JD, et al. ARN-509: a novel antiandrogen for prostate cancer treatment. *Cancer Res*. 2012;72:1494–1503.
17. Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *Eur Urol*. 2016;70:963–970.
18. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378:1408–1418.
19. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187–1197.
20. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424–433.
21. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. *J Clin Oncol*. 2016;34:2098–2106.
22. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378:2465–2474.
23. Fizazi K, Albiges L, Loriot Y, Massard C. ODM-201: a new-generation androgen receptor inhibitor in castration-resistant prostate cancer. *Expert Rev Anticancer Ther*. 2015;15:1007–1017.
24. Moilanen AM, Riikonen R, Oksala R, et al. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. *Sci Rep*. 2015;5:12007.
25. Borgmann H, Lallous N, Ozistanbullu D, et al. Moving towards precision urologic oncology: targeting enzalutamide-resistant prostate cancer and mutated forms of the androgen receptor using the novel inhibitor darolutamide (ODM-201). *Eur Urol*. 2018;73:4–8.
26. Shore ND. Darolutamide (ODM-201) for the treatment of prostate cancer. *Expert Opin Pharmacother*. 2017;18:945–952.
27. Fizazi K, Massard C, Bono P, et al. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. *Lancet Oncol*. 2014;15:975–985.
28. Massard C, Penttinen HM, Vjaters E, et al. Pharmacokinetics, antitumor activity, and safety of ODM-201 in patients with chemotherapy-naive metastatic castration-resistant prostate cancer: an open-label phase 1 study. *Eur Urol*. 2016;69:834–840.
29. Xie W, Regan MM, Buyse M, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol*. 2017;35:3097–3104.
30. Schweizer MT, Zhou XC, Wang H, et al. Metastasis-free survival is associated with overall survival in men with PSA-recurrent prostate cancer treated with deferred androgen deprivation therapy. *Ann Oncol*. 2013;24:2881–2886.
31. Antonarakis ES, Chen Y, Elsamanoudi SI, et al. Long-term overall survival and metastasis-free survival for men with prostate-specific antigen-recurrent prostate cancer after prostatectomy: analysis of the Center for Prostate Disease Research National Database. *BJU Int*. 2011;108:378–385.
32. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379:39–46.
33. Beaver JA, Kluetz PG, Pazdur R. Metastasis-free survival—a new end point in prostate cancer trials. *N Engl J Med*. 2018;378:2458–2460.