Androgen receptor (AR) signaling is essential for cancer cell proliferation throughout much, if not all, of the course of a patient's journey through prostate cancer. Discovery of the AR in the late 1960s prompted development of antiandrogen drugs that competitively inhibit binding of androgens to the AR ligand-binding domain (LBD), leading to conformational changes in AR that disrupt its function. Between 1989 and 1996, flutamide, bicalutamide, and nilutamide were approved by the US Food and Drug Administration (FDA) to be used in combination with chemical or surgical castration. Of these three first-generation nonsteroidal antiandrogens, bicalutamide is the most commonly used because of its once-per-day pharmacokinetics, tolerability, and efficacy. Bicalutamide binds the LBD, recruits corepressors to the AR, and interferes with recruitment of coactivators. Despite the use of these agents, drug resistance and disease progression remain a challenge in disease management. Common mechanisms of resistance to bicalutamide include induction of wild-type AR expression, which leads to increased nuclear AR protein levels that cause bicalutamide to act as an AR agonist, increased AR coactivator expression, and development of mutations in the AR LBD-confering antagonist-to-agonist switch on bicalutamide.

In an effort to develop next-generation AR-targeted therapy, a drug screen was used to evaluate agents that inhibit AR activity in the setting of AR receptor overexpression. In preclinical studies, enzalutamide, an AR inhibitor, demonstrated favorable pharmacokinetics and significantly higher affinity for the AR than bicalutamide. Unlike bicalutamide, enzalutamide lacked agonist activity for the wild-type AR, did not recruit AR coactivators, and inhibited AR binding to DNA, which leads to reduced expression of androgen-dependent genes. On the basis of findings from the AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy) trial showing a significant improvement in overall survival (OS) compared with placebo in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel (hazard ratio [HR], 0.63; 95% CI, 0.53 to 0.75), the FDA approved enzalutamide for men with metastatic CRPC who had received prior chemotherapy. A subsequent phase III trial of enzalutamide versus placebo in patients with metastatic CRPC who have not previously been treated with docetaxel, the PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer) trial, demonstrated that enzalutamide resulted in an 81% reduction in risk of radiographic progression and a 29% reduction in the risk of death.

To illustrate the natural history of prostate cancer relative to various treatments and to assess the response status to different therapies (ie, antiandrogens), a conceptual description of the natural history of prostate cancer referred to as the "clinical states model" has been proposed (Fig 1). In this model, the history of a patient's prostate cancer is described as progression through a series of states from diagnosis to death. Each stage represents a clinically significant category, and progression from one state to another reflects a change in prognosis generally prompting a change in therapy.

In the article accompanying this editorial, Penson et al present results of the STRIVE (Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men With Prostate Cancer) trial, a study in chemotherapy-naive men with metastatic CRPC or nonmetastatic CRPC comparing progression-free survival (PFS) with enzalutamide 160 mg/d versus bicalutamide 50 mg/d administered as secondary hormonal therapy. Data from this trial clearly validate the preclinical studies noted earlier that demonstrate the superiority of enzalutamide over bicalutamide as an antiandrogen. With respect to the primary end point, enzalutamide, when compared with bicalutamide, reduced the risk of death or progression, which was defined as prostate-specific antigen (PSA) progression or investigator assessed radiographic progression by 76% (HR, 0.24; 95% CI, 0.18 to 0.32). In addition, the secondary end points of PSA progression, proportion of patients with a significant (>50%) PSA decrease, and radiographic PFS, strongly favored enzalutamide. In the 139 patients with nonmetastatic CRPC, the median radiographic PFS was not yet reached in either arm. However, enzalutamide reduced risk of radiographic progression by 76% (HR, 0.24; 95% CI, 0.10 to 0.56) compared with bicalutamide. In the 257 patients with metastatic CRPC, enzalutamide reduced the risk of radiographic progression by 68%. Median radiographic PFS was not reached with enzalutamide and was 8.3 months with bicalutamide (HR, 0.32; 95% CI, 0.21 to 0.50; P < .001).

One should consider the 50 mg/d bicalutamide dosing that was chosen for the study when interpreting these findings. Bicalutamide has been FDA-approved for men with nonmetastatic CRPC at this dose and when used in conjunction with androgen deprivation therapy (ADT). It is possible that bicalutamide 50 mg/d may be insufficient to block the AR amplification observed in CRPC, and a higher dose of 150 mg/d may have resulted in improved efficacy of the bicalutamide control arm.

These results are compelling, but how can these data be used in clinical practice and how might these results influence the future
landscape of prostate cancer trials? In the bicalutamide arm of the STRIVE study (including both metastatic and nonmetastatic patients), PSA progression occurred at a median of 8.3 months, and median radiographic PFS was nearly 11 months. This time span is considered clinically meaningful, particularly in light of the generally favorable bicalutamide adverse effect profile characterized by less fatigue compared with enzalutamide (all grades, enzalutamide 38% and bicalutamide 28%). Assuming that enzalutamide activity is not diminished by prior bicalutamide, should sequential bicalutamide followed by enzalutamide be considered in patients with minimal or no metastatic disease who will still have an opportunity to receive enzalutamide after progressing on bicalutamide? Approximately 65% of men in both arms of the PREVAIL trial previously received treatment with one line of antiandrogen, and 20% received at least two or more prior antiandrogens, suggesting resistance to antiandrogens at the time of study entry. However, it is unclear what proportion of these men was truly resistant (specifically, the percentage of men who received antiandrogen therapy to prevent flare associated with ADT and the duration of antiandrogen treatment are unknown). Investigators in the AFFIRM trial reported that almost 50% of patients had received more than two prior hormonal regimens, likely including an antiandrogen. Similarly, the potent androgen synthesis inhibitor abiraterone was more active than prednisone, regardless of prior antiandrogen treatment.15 Therefore, from phase III trials with next-generation AR-targeted therapy, there is no clear sign of decreased activity after treatment with first-generation antiandrogens. A second contemporaneous trial of enzalutamide versus bicalutamide (the TERRAIN [A Study of Enzalutamide Versus Bicalutamide in Castrate Men With Metastatic Prostate Cancer] study) was recently reported that enrolled only patients with metastatic CRPC and no prior bicalutamide.16 In the TERRAIN study, median time to PSA progression with enzalutamide was 19.4 months compared with 11.2 months in the PREVAIL trial in which patients were allowed to have prior antiandrogens. Significant differences in baseline characteristics of patients in these two studies (patients in the PREVAIL study had higher PSAs and lower albumin levels) could also have been significant factors that contributed to differences noted across studies rather than prior antiandrogen therapy. Data on mechanisms of resistance may also suggest a benefit to sequential therapy. Although resistance to bicalutamide may emerge through acquired mutations in the AR LBD, enzalutamide is active in the setting of the W742C bicalutamide-activated mutation, thereby mitigating this potential downside to first-line use of bicalutamide. Development of AR splice variants, such AR-V7, mutations in AR, and promiscuous activity of the glucocorticoid receptor can lead to enzalutamide resistance.17,18 When this occurs, no other approved hormonal agents have clear activity,18 and treatment generally proceeds to chemotherapy. Thus, sequential therapy with bicalutamide before enzalutamide may be of potential benefit in delaying time to enzalutamide resistance.

Using the most effective antiandrogen in the setting of nonmetastatic CRPC is valid. However, a more compelling question is whether meaningful clinical benefit occurs by delaying the development of metastases. Before the advent of next-generation AR-targeted therapies, bone-targeted therapies such as denosumab were tested in the nonmetastatic CRPC state to delay morbidity as a result of skeletal metastasis and to delay the need for chemotherapy. Ultimately, denosumab was not approved by the FDA in this population because of the potential for osteonecrosis of the jaw, a treatment-related delay of 4 months in the development of metastasis (marginal clinical significance), and no OS benefit.19 Unlike denosumab, using next-generation AR targeted therapy in this setting may offer substantial benefit with respect to metastasis-free survival that may have an impact on OS, but this remains to be confirmed.

The potential benefit from improving the metastasis-free survival in patients with nonmetastatic CRPC was recently modeled by Scher et al.20 By using published clinical trial and observational data, the investigators estimated the rate of progression between different prostate cancer clinical states and the mortality within each clinical state. By using this model, the authors were able to project the impact of a novel therapy that increased metastasis-free survival in patients with nonmetastatic CRPC or that increased OS in patients with metastatic CRPC. Improving metastasis-free survival by 25% in patients with nonmetastatic CRPC led to a decline in metastatic CRPC mortality over time as the prevalence of patients with metastatic CRPC declined. By comparison, improving OS by 25% in patients with metastatic CRPC caused a smaller impact on metastatic CRPC mortality over time as the prevalence of patients with metastatic CRPC increased and a new equilibrium set in among patients with metastatic CRPC. In light of this model, the 76%
improvement in PFS observed in the STRIVE study could theoretically improve prostate cancer OS as the number of patients progressing to metastatic CRPC significantly decreases. A potential caveat to this model and to the clinical use of enzalutamide and other next-generation AR-targeted therapies in nonmetastatic CRPC is the possibility that using these agents earlier may decrease survival in the metastatic CRPC state, mitigating some of the benefits of early therapy. Currently, there are no approved AR-targeted therapies for use after enzalutamide, which leads to fewer therapeutic options for men with metastatic CRPC after enzalutamide therapy. In addition, some preclinical studies suggest that resistance to AR-targeted therapy may lead to decreased activity of subsequent docetaxel (but probably not cabazitaxel), although the clinical significance of these findings remains unknown. Therefore, considering the agents available in 2016, men who ultimately progress from nonmetastatic CRPC to metastatic CRPC while being treated with next-generation AR-targeted therapies will need to be aware that additional hormone therapy may not necessarily be available in the setting of metastasis. Currently there are three randomized phase III trials for patients with nonmetastatic CRPC: enzalutamide versus placebo (NCT02003924; Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer [PROSPER]), apalutamide (ARN-509) versus placebo (NCT01946204; A Study of ARN-509 in Men With Non-Metastatic Castration-Resistant Prostate Cancer [SPARTAN]), and ODM-201 versus placebo (NCT02200614; Efficacy and Safety Study of BAY1841788 (ODM-201) in Men With High-Risk Non-Metastatic Castration-Resistant Prostate Cancer [ARAMIS]). By using metastasis-free survival as the primary end point and OS as a secondary end point, these trials can validate compelling observations seen in the STRIVE trial and help to clarify the relationship between increasing duration of time in the nonmetastatic CRPC state and increasing OS. Beyond treatment with next-generation AR-targeted therapy, future drug development with nonmetastatic CRPC should be focused on rational combinations with minimal toxicity. Immune-based therapies have a strong preclinical rationale for combining with AR-directed therapy by increasing production of naïve T cells and increasing the number of tumor-infiltrating lymphocytes. In addition, completed phase II studies suggest benefit from early initiation of combined immunotherapy and androgen treatment, which provides support for studies of enzalutamide and immune therapy in patients with nonmetastatic CRPC.

The dramatic improvement in metastasis-free survival in those receiving enzalutamide compared with bicalutamide begs us to re-examine the role of hormonal therapy earlier in the disease continuum. Men with biochemical recurrence represent a population at increased risk for cancer-related morbidity and mortality compared with patients with high-risk localized disease that may never develop biochemical recurrence. Patients with biochemical recurrence have variable prognoses with metastasis-free survival ranging from 1 to more than 15 years, depending on clinical parameters such as PSA doubling time, all of which complicate potential trial design. Using genomic classifiers may further risk stratify patients with biochemical recurrence and enrich trials for high-risk patients, shortening the time to reach a metastasis-free survival end point and decreasing the number of patients needed to see a meaningful clinical benefit. A coordinated effort led by the ICECaP (Intermediate Clinical Endpoints in Cancer of the Prostate) working group is currently underway to develop a surrogate for OS by correlating intermediate clinical end points such as metastasis-free survival with OS by using individual patient data gathered from 43 randomized controlled prostate cancer trials with an OS end point. A phase III trial evaluating enzalutamide, leuprolide, or the combination (the EMBARK trial; NCT02319837; Safety and Efficacy Study of Enzalutamide Plus Leuprolide in Patients With Nonmetastatic Prostate Cancer) is now underway. The EMBARK study will enroll 1,860 patients with nonmetastatic hormone-sensitive prostate cancer and PSA doubling time of less than 9 months with a metastasis-free survival primary end point and an OS secondary end point to define the benefit of enzalutamide alone or as part of a contemporary complete androgen blockade regimen.

Does data from the STRIVE study allow us to contemplate the use of next-generation AR-targeted therapy as adjuvant therapy, perhaps as part of a multitargeted approach to achieve improved overall patient survival? Emerging data quantifying the accumulation of genomic aberrations as prostate cancer evolves from localized to lethal metastatic disease lend preclinical support to the potential clinical benefit of suppressing clonal evolution early in the cancer disease process. Early use of hormonal therapy is not in itself a guarantee of success. In 1995, the Early Prostate Cancer program randomly assigned 8,113 men with localized prostate cancer (most of whom had primary therapy) who were participants in three double-blind placebo-controlled trials to adjuvant bicalutamide 150 mg/d or to placebo, with primary study end points of PFS and OS. After nearly 10 years of follow-up, there was no improvement in OS for the population as a whole (HR, 1.01; P = .77). Were these studies negative because the drug was suboptimal? Or were patients not properly selected? The potential benefit of contemporary agents compared with older therapies is clear, based on STRIVE findings, whereas refinements in clinical predictors of outcome and increased accessibility of genomic profiling will allow for selection of patients who may benefit most from intervention. The substantial survival benefit seen when docetaxel is administered with initiation of ADT for metastatic hormone-sensitive prostate cancer rather than later in the disease course suggests that next-generation AR-targeted therapy in combination with chemotherapy is worthy of consideration in the early disease setting.

The cost to society and the impact of early systemic therapy on patient quality of life are factors that need to be carefully accounted for in the design of future clinical trials. However, in 2016, with a new generation of active treatments and the availability of next-generation sequencing, the tools may finally be at hand to strive toward a cure in early, aggressive prostate cancer.

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