Evolving Evidence-Based Treatment Paradigms for Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC)

In 2018, there will be an estimated 164,690 new cases of prostate cancer (PC) in the U.S. and approximately 29,430 patients will die of the disease, making it the third-leading cause of cancer death in men (American Cancer Society [ACS], 2018). The majority of men with PC are treated with curative intent (i.e., with radical prostatectomy or radiation therapy) with good outcomes, but a fraction of men with locoregional PC will develop progressive disease. Men who have initial PSA/biochemical recurrence after curative treatment are a heterogeneous group of individuals with good overall prognosis, including a median metastasis-free survival (MFS) >8 years and a median overall survival (OS) of >23 years (Rozet et al., 2016).

Approximately 10%-20% of prostate cancer patients develop castration-resistant PC (CRPC) within approximately 5 years of follow-up. Decisions about clinical management (i.e., when to start treatment) are challenging because it is unclear which patients will have shorter versus longer survival, and metastatic disease is not always reliably detected with imaging (Rozet et al., 2016).

Multiple new targeted agents, including immunotherapy, second-generation hormone therapy, and androgen biosynthesis inhibitors have been recently approved. Two recently published studies (PROSPER and SPARTAN) have changed the standard of care for patients with nmCRPC.

TARGET AUDIENCE

The target audiences for these activities are urologists, medical oncologists, urology/oncology nurses, advanced practice registered nurses and nurse navigators.

EDUCATIONAL OBJECTIVES

- Describe new data regarding the evidence-based management of patients with nmCRPC prostate cancer and apply it to practice
- Identify ongoing late-phase clinical trials in castration-resistant prostate cancer
- Discuss implications of decisions regarding timing and treatment sequencing for patients with nmCRPC on subsequent therapy

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JOINT ACCREDITATION STATEMENT

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Release date: April 15, 2019
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Estimated time to complete activity: 45 minutes

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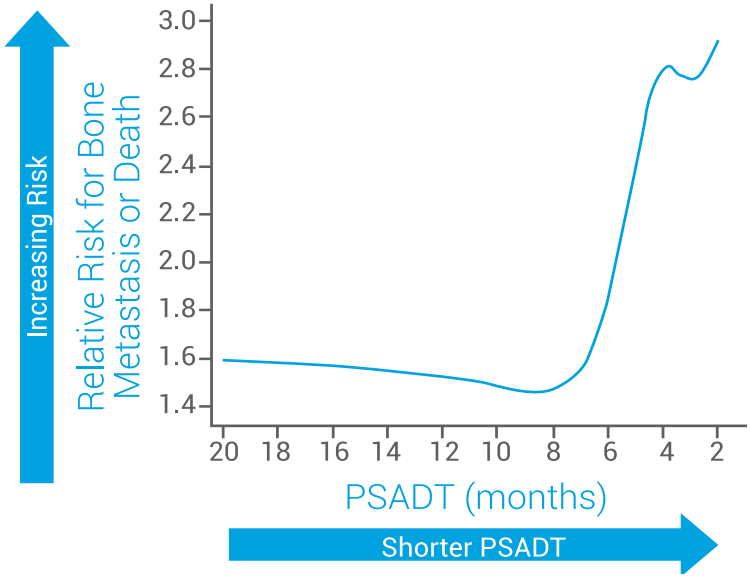
Non-metastatic castration-resistant prostate cancer (nmCRPC) is a biochemical recurrence of prostate cancer following primary treatment. nmCRPC is characterized by rising prostate-specific antigen (PSA) levels in patients with castrate levels of testosterone and no radiographic evidence of distant metastatic disease. Most patients with nmCRPC eventually develop terminal metastatic castration-resistant prostate cancer (mCRPC). The risk of disease progression or death is proportionate to the patient's prostate-specific antigen doubling time (PSADT); patients with a shorter PSADT are at greater risk. In an exploratory analysis of baseline PSADT in men with nmCRPC, Smith et al (2013) demonstrated that in the placebo group the relative risk for bone metastasis-free survival (MFS) over PSADT significantly increased when PSADT decreases to less than 8 months (see Figure, adapted from Smith et al, 2013).

Three recent Phase 3 placebo-controlled randomized trials (SPARTAN, PROSPER, and ARAMIS) of second-generation androgen-directed therapies (apalutamide, enzalutamide, and darolutamide) are changing the standard of care for patients with nmCRPC (Smith et al, 2018; Hussain et al, 2018; Fizazi et al; 2019). In all three trials, patients received the trial drug or placebo in addition to androgen deprivation therapy (ADT). Based on the findings of Smith et al (2013), indicating that shorter PSADT is a predictor of risk for bone metastasis, patient criteria in all three studies included a PSADT of 10 months or less. These three trials, all of which met their primary endpoints for MFS, are described below.



SPARTAN TRIAL (APALUTAMIDE)

The SPARTAN trial randomly assigned 1,207 patients with nmCRPC to receive either apalutamide plus ADT (n=806) or placebo plus ADT (n=401). Patient demographics were relatively evenly distributed across arms. Average age of patients was 74 years (range 48–97 years). Patient data were stratified by: (1) PSA doubling time equal to or less than 6 months versus greater than 6 months; (2) whether they were receiving bone-sparing agents; and (3) classification of local or regional nodal disease N0 (no local or regional nodal disease) or N1 (malignant pelvic lymph nodes measuring less than 2 cm that were located below the aortic bifurcation) (Smith et al, 2018; Small et al, 2018).

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint was MFS, defined as the time from randomization to the first detection of distant metastasis on imaging studies or death from any cause. Secondary endpoints included time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy (Smith et al, 2018).

Outcomes and Adverse Events

The SPARTAN trial demonstrated that the addition of apalutamide to ADT markedly improves MFS compared to ADT with placebo (40.5 months vs. 16.2 months, respectively) in all subgroups, with a hazard ratio for metastasis or death of 0.28 (95% confidence interval 0.23–0.35). Median duration of follow-up was 20.3 months. Patients treated with apalutamide experienced higher rates of adverse events compared to patients in the placebo arm. Adverse events considered by the investigators to be related to increased toxicity from apalutamide compared to placebo were fatigue (30.4% vs. 21.1%), rash (23.8% vs. 5.5%), falls (15.6% vs. 9.0%), fracture (11.7% vs. 6.5%), hypothyroidism (8.1% vs. 2.0%), and seizure (0.2% vs. 0%). Rash was the only side effect of apalutamide that is not typically seen in other drugs used to treat nmCRPC. In all patient subgroups, side effects did not negatively impact quality of life and the addition of apalutamide to ADT resulted in greater than 70% reduction in risk of metastasis or death.

PROSPER TRIAL (ENZALUTAMIDE)

The PROSPER trial was modeled similar to the SPARTAN

trial; 1,401 patients were randomly assigned to receive either enzalutamide plus ADT (n=933) or placebo plus ADT (n=468) and median age of patients was approximately 74 years (range 50–95 years) (Hussain et al, 2018). In this study, patient data were stratified by: (1) PSA doubling time equal to or less than 6 months versus greater than 6 months and (2) baseline use of bone-sparing agents (Hussain et al, 2018). The PROSPER trial demonstrated that the addition of enzalutamide to ADT markedly improves MFS compared to ADT with placebo (36.6 months vs. 14.7 months, respectively) in all subgroups, with a hazard ratio for metastasis or death of 0.29 (95% confidence interval 0.24–0.35).

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint was MFS, defined as the time from randomization until death or evidence of progression on radiographic imaging studies conducted every 16 weeks (Hussain et al, 2018). Secondary endpoints included safety, time to PSA progression, time to use of new antineoplastic therapy, overall survival, PSA response, and quality of life (Hussain et al, GU ASCO, 2018).

OUTCOMES AND ADVERSE EVENTS

In the PROSPER study, the most common side effect of enzalutamide was fatigue, occurring in 32.6% compared to 13.8% in the placebo group (Hussain et al, 2018). Other adverse events occurring in at least 10% of patients receiving enzalutamide and at least a 2% higher rate in the enzalutamide arm than in the placebo arm were hot flashes (13% vs. 8%), nausea (11% vs. 9%), hypertension (12% vs. 5), falls (11% vs. 4%), dizziness (10% vs. 4%), decreased appetite (10% vs. 4%); major cardiovascular events occurred in 5% of patients receiving enzalutamide and 3% of patients receiving placebo; however, in both arms cardiovascular events occurred more frequently in patients who had a baseline history of cardiovascular disease, hypertension, diabetes, or high cholesterol, or who were older than 75 years (Hussain et al, 2018). Side effects were managed without significantly impacting quality of life.

ARAMIS TRIAL (DAROLUTAMIDE)

Data from a third randomized Phase 3 study in patients with nmCRPC, the ARAMIS trial, was recently presented at the Genitourinary Cancers Symposium in February 2019. The ARAMIS trial studied the efficacy and safety of darolutamide in patients with nmCRPC (Fizazi et al, 2018; Fizazi et al, 2019). In the ARAMIS trial, 1,509 patients were randomly assigned to receive darolutamide plus ADT (n=955) or placebo plus ADT (n=554) for treatment of nmCRPC. Darolutamide was administered at a dose of 600 mg (two 300 mg tablets) twice-daily. Patient data were stratified by: (1) PSA doubling time (≤6 months or >6 months) and (2) use of osteoclast-targeted therapy.

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint was MFS assessed by independent central review of radiographic imaging every 16 weeks (Fizazi et al, 2019). Secondary endpoints include overall survival, times to pain progression (assessed by Brief Pain Inventory), first cytotoxic chemotherapy and first symptomatic skeletal event, as well as safety profile (Fizazi et al, 2019).

OUTCOMES AND ADVERSE EVENTS

The ARAMIS trial demonstrated that the addition of darolutamide to ADT markedly improves MFS compared to ADT with placebo in all subgroups (40.4 months vs. 18.4 months, respectively) with a hazard ratio for metastasis or death of 0.41 (95% confidence interval 0.34–0.50) (Fizazi K et al, 2019). Fatigue was the only adverse event that occurred in more than 10% of patients and all adverse events that commonly occur in patients treated with androgen receptor inhibitors (fracture, falls, seizures, weight decrease, hypertension, and cognitive disorder) were comparable in patients in both arms (Fizazi K et al, 2019).

Phase 3 Trials of Androgen-Directed Therapies in Addition to Androgen Deprivation Therapy for Treatment of Non-Metastatic Castration-Resistant Prostate Cancer

	SPARTAN trial	PROSPER trial	ARAMIS trial
Number of patients	1,207	1,401	1,509
Study drug	apalutamide	enzalutamide	darolutamide
Daily dose	240 mg	160 mg	1200 mg
Primary endpoint MFS: study drug vs. placebo (months)	40.5 vs. 16.2	36.6 vs. 14.7	40.4 vs. 18.4
Hazard ratio for metastasis or death [95% confidence interval]	0.28 [0.23–0.35]	0.29 [0.24–0.35]	0.41 [0.34–0.50]
FDA approval for treatment of nmCRPC	February 14, 2018	July 13, 2018	Submitted February, 2019

(Smith et al, 2018; Hussain et al, 2018; Fizazi et al; 2019; Targeted Oncology, 2019)

TIMING AND SEQUENCING OF THERAPIES

Optimal sequencing of prostate cancer treatments has not yet been defined in randomized trials. Numerous trials have demonstrated benefits of single drugs administered prior to, during, or after chemotherapy for prostate cancer. Enzalutamide and abiraterone are the most common first-line therapies used in metastatic disease; both increase overall survival times in chemotherapy-naïve patients with mCRPC (Beer et al, 2014; Beer et al, 2017; Ryan et al, 2013). However, their efficacy when used sequentially (i.e., abiraterone after enzalutamide, enzalutamide after abiraterone, or either drug repeated) for treatment of mCRPC is significantly reduced (Azad et al, 2015; Beer et al, 2014; Ryan et al, 2013). Response rates following first use of either drug for mCRPC are typically in the 60% to 80% range and decrease to as low as 10% to 30% following sequential use; PSA progression-free survival decreases from approximately 11 months down to only 3 to 4 months.

Further studies are needed to assess whether changes in timing or sequencing of therapies can increase response rates and survival times in late-stage mCRPC. Specifically, investigations should focus on whether use of specific drugs for the treatment of nmCRPC will decrease their effectiveness later when used to treat mCRPC and whether specific timing or sequencing can achieve maximum benefit. An ongoing international prospective IRONMAN registry is gathering information about patient experiences with advanced prostate cancer treatments and side effects. This data will provide insight to guide future studies [TrueNTH, n.d.].

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