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Addition of Enzalutamide to Leuprolide and Definitive Radiation Therapy Is Tolerable and Effective in High-Risk Localized or Regional Nonmetastatic Prostate Cancer: Results From a Phase 2 Trial



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Background: Enzalutamide is an antiandrogen used to treat both metastatic and nonmetastatic prostate cancer. Here we present results from a phase 2 trial designed to determine the safety, tolerability, and efficacy of adding enzalutamide to standard androgen deprivation therapy with radiation therapy in high-risk localized or regional, nonmetastatic patients with prostate cancer.

Methods and Materials: Enrollment criteria included at least 2 of the following: stage cT3a/b, prostate specific antigen (PSA) ≥ 20 ng/mL, Gleason grade 8 to 10, $\geq 33\%$ core involvement on biopsy, or pelvic lymph node involvement on computed tomography or magnetic resonance imaging. Patients with metastatic disease were excluded. All patients received 24 months of leuprolide and enzalutamide, and 5 weeks of intensity modulated radiation therapy followed by a brachytherapy boost. Adverse events (AE), PSA, testosterone, and basic laboratory tests were then followed for up to 36 months. Primary outcomes were safety and tolerability and PSA complete response rate (PSA-CR, defined as PSA ≤ 0.3). Secondary outcomes included time to biochemical recurrence (BCR; nadir + 2 ng/mL).

Results: Sixteen patients were enrolled; 2 were ineligible and 3 withdrew before starting treatment. Median age at enrollment was 69.0 years (interquartile range [IQR] 11.5). Median treatment duration was 24.0 months (IQR 11.9). Median follow-up time was 35.5 months (IQR 11.2), and 9 of 11 (81.8%) patients completed the 36 months of follow-up. One of 11 (9%) patients had grade 4 AE (seizure), and no grade 5 AE were reported. Four of 11 (36.4%) patients had grade 3 AE, such as erectile dysfunction and hot flashes. All patients achieved PSA-CR, and median time to PSA-CR was 4.2 months (IQR 1.4). At 24 months follow-up, 0 of 11 (0%) patients had a biochemical recurrence. At 36 months, 1 of 9 (11.1%) patient had a biochemical recurrence. Of note, this patient did not complete the full 24 months of enzalutamide and leuprolide due to AEs.

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Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Conclusions: Enzalutamide in combination with standard androgen deprivation therapy and radiation therapy was well-tolerated and effective warranting further study in a randomized controlled trial.

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Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy among men in the United States, with an estimated 250,000 new cancer cases in 2021.¹ Approximately 15% of individuals with localized disease are identified as “high-risk” for disease recurrence.^{2,3} Multiple different classification systems exist, such as the D’Amico and National Comprehensive Cancer Network classification systems, which use prostate specific antigen (PSA) recurrence as a primary end point and defining high-risk disease as at least greater than clinical cT2c, Gleason score of 8 or more, or a PSA greater than 20 ng/mL.^{3–6} Definitive radiation therapy (RT) with the addition of 18 to 36 months of androgen deprivation therapy (ADT) is a primary option for patients with high-risk localized or regional PCa, which has been shown to significantly improve disease control and PCa-specific mortality outcomes compared with RT alone or RT with ADT; however, there is room for improvement, with recent data reporting 8-year biochemical recurrence rates of 20% to 50% and 8-year overall survival (OS) reported between 70% to 80%.⁷

Multiple trials have sought to improve survival outcomes of ADT with RT through the addition of additional therapeutic agents. For example, the radiation therapy oncology group (RTOG) 9902 trial did not show clinical benefit, including OS, of addition of adjuvant paclitaxel, estramustine, and etoposide chemotherapy after combined ADT and RT in high-risk PCa.⁸ Similarly, a study by D’Amico and colleagues this year demonstrated no improvement in OS from addition of adjuvant docetaxel after combined ADT and RT in nonmetastatic unfavorable-risk PCa⁹; in contrast, the RTOG 0521 trial demonstrated improvement in OS from addition of adjuvant docetaxel after combined ADT and RT in high-risk PCa.¹⁰ Combination therapy of luteinizing hormone releasing hormone (LHRH)-agonist therapy and antiandrogens leading to greater androgen suppression has been shown to improve clinical outcomes in patients with castrate-sensitive metastatic PCa (CSPC). In a large phase 3 trial, Crawford et al demonstrated improved clinical response, progression free survival, and OS in metastatic PCa patients receiving the combination of leuprolide and flutamide, a nonsteroidal androgen receptor (AR) antagonist, compared with leuprolide alone.¹¹ The authors noted in this study that the greatest OS benefit was seen in patients with limited disease. Similarly, addition of abiraterone to ADT for patients was investigated in the STAMPEDE trial, demonstrating favorable overall survival in the combination therapy compared with ADT alone.¹²

Enzalutamide is a second-generation nonsteroidal AR antagonist, which unlike first-generation antagonists, affect key components of AR signaling including androgen binding, nuclear translocation, and DNA binding of AR.¹³ Enzalutamide also has high affinity for AR, with preclinical studies demonstrate 9-fold greater affinity compared with first-generation antagonist bicalutamide.¹⁴ In phase 3 clinical trials, enzalutamide in combination with ADT improved overall survival in patients compared with placebo in castrate-resistant PCa (CRPC).^{15,16} Furthermore, enzalutamide was found to be active in men with hormone-naïve PCa, with 92.5% of men demonstrating a PSA decline of 80% or more.^{17,18} Of note, 25% of patients in this study underwent radiation therapy in addition to enzalutamide, which was well-tolerated.

We hypothesize that the additional androgen receptor signaling inhibition provided by enzalutamide when combined with standard ADT can reduce recurrence rates in localized or regional nonmetastatic PCa patients receiving definitive radiation therapy. In this phase 2 trial, we aimed to assess feasibility, safety, and tolerability of combining enzalutamide to ADT in such patients undergoing definitive radiation therapy and assess PSA response and recurrence.

Methods and Materials

Ethical approval

This clinical study (ClinicalTrials.gov Identifier: NCT02508636) was approved by the UCSF Institutional Review Board and was conducted in accordance with Good Clinical Practice. The study was monitored by the UCSF Helen Diller Family Comprehensive Cancer Center Data and Safety Monitoring Committee in accordance with the National Cancer Institute-approved Data and Safety Monitoring Plan. Informed consent was obtained from all individual participants included in the study before any study related procedures. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Eligibility criteria

The patients eligible for inclusion had high-risk localized or regional PCa, defined as having at least 2 of the following criteria: stage cT3a/b disease as determined by transrectal ultrasound of the prostate, PSA \geq 20 ng/mL,

Gleason grade 8 to 10, $\geq 33\%$ core involvement on prostate biopsy; or ≥ 1 cm pelvic lymph node(s) identified on computed tomography (CT) or magnetic resonance imaging (MRI). Staging scans at diagnosis included bone scan or NaF positron emission tomography/CT scan, and pelvic and prostate MRI. Patients with evidence of metastatic disease were excluded. No prior androgen deprivation therapy (ADT) was permitted. Patients with history of bilateral orchiectomies for other reasons were excluded. Patients with the following conditions were excluded: concomitant malignancies within the past 3 years, adrenal disorders and chronic treatment with glucocorticoids within the past 1 year, chronic renal disease (with serum creatinine >2.0 mg/dL, and confirmed by creatinine clearance <40 mL/min), chronic liver disease (with bilirubin $>1.5 \times$ the upper limit of normal, ALT or AST $>2 \times$ upper limit of normal), active or uncontrolled viral hepatitis, history of seizure or condition that may predispose to seizure, and clinically significant cardiovascular disease (myocardial infarction within 6 months, uncontrolled angina within 3 months, congestive heart failure New York Heart Association class 3 or 4, clinically significant ventricular arrhythmias, Mobitz II second degree or third degree heart block without pacemaker, and uncontrolled hypertension). All patients had Eastern Cooperative Oncology Group (Zubrod) performances scores of 0 to 2 at enrollment. Enrollment had to be completed within 180 days of diagnosis.

Study design and treatment

We performed a single arm, single site, phase 2 clinical trial. The therapeutic regimen is summarized in Fig 1. Day 0 was defined as the first day of administration of leuprolide, an LHRH agonist. Leuprolide was administered via intramuscular injections in 1-month, 3-month, 4-month, or 6-month formulations. Enzalutamide administration was initiated within 7 days of leuprolide initiation, and 160 mg of enzalutamide were given orally each day. The goal was for all patients to receive a total of 24 months of both leuprolide and enzalutamide. All patients then had fiducial marker placement between days 31 to 37. Radiation therapy was then initiated between days 53 to 67. All patients received conventional whole pelvis intensity modulated radiation therapy or volumetric modulated arc therapy for 5 weeks, 45 Gy total. Patients with N1 disease also received an intensity modulated radiation therapy or volumetric modulated arc therapy boost to involved nodes to a total dose of 55 to 59.4 Gy in 25 to 33 fractions using either sequential or integrated boost technique. External beam RT was followed by a high-dose rate prostate brachytherapy boost of 15 Gy in 1 fraction. External beam radiation planning goals included planning target volume (PTV) V100% $>95\%$; rectum V40Gy $<20\%$, bladder V40Gy $<30\%$, which were met in all cases.

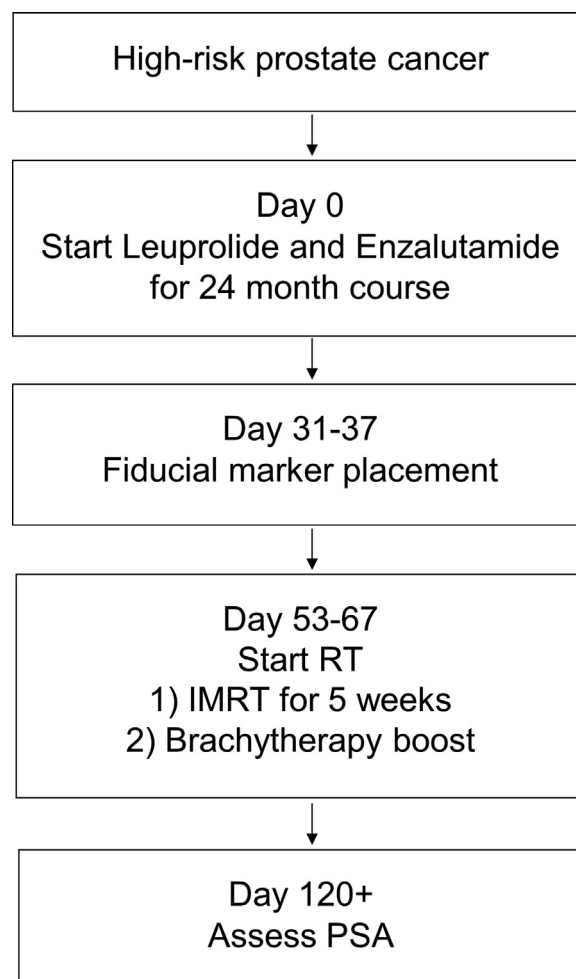


Fig. 1 Androgen deprivation therapy and radiation therapy study protocol. *Abbreviations:* IMRT = intensity-modulated radiation therapy; PSA = prostate specific antigen; RT = radiation therapy.

Brachytherapy planning goals included PTV coverage $>95\%$, rectum V75% <1 cm³, bladder V75% <1 cm³, and urethra V120% = 0. PTV margins were 5 to 7 mm for prostate or seminal vesicles, 5 to 7 mm for involved nodes, 5 mm for elective lymph nodes, and 0 mm for brachytherapy. Image-guided radiation therapy was performed using daily cone beam CT with prostate fiducial marker alignment. All patients receiving external beam RT were instructed to use an enema and drink fluid before CT simulation to achieve a comfortably full bladder and empty rectum; enema was not required during daily radiation delivery. PSA, testosterone, and basic laboratory tests (CBC, CMP) were monitored throughout the study and for a total of 36 months of follow-up (at enrollment, 6 weeks, 3-4 months, 6 months, 12 months, 18 months, 24 months, and 36 months). Changes in HgbA1c, fasting glucose, liver enzymes, lipid, and cholesterol levels were assessed at enrollment, 12, and 24 months. All adverse events were recorded weekly during treatment, then every 3 to 6 months for up to 24 months after radiation therapy

and finally at 36 months after radiation therapy. Adverse events were defined according to Common Terminology Criteria for Adverse Events version 4.0 criteria. Changes in patient reported quality of life were measured with the use of the Expanded Prostate Cancer Index Composite (EPIC) score, the Patient-Reported Outcomes Measurement Information System (PROMIS), and the EuroQol-5D (EQ-5D) score at enrollment, 12 months, and 24 months. Sample size was determined based on power calculations for the primary objectives of PSA-CR and toxicity, with an initial enrollment goal of 53 patients with high-risk localized or regional PCa.

Study objectives

The primary objectives of this study were to determine the rate of acute toxicity (≤ 90 days within the completion of radiation therapy), late toxicity (≥ 91 days within the completion of radiation therapy to 24 months of follow-up), and to determine the PSA complete response rate (PSA-CR), defined as PSA nadir ≤ 0.3 ng/mL,¹⁹ in these patients at 120 days after initiation of ADT. Secondary objectives included determining PSA nadir, evolution of testosterone levels and changes in HgbA1c, fasting glucose, insulin, lipid, and cholesterol levels during and after treatment, and time to BCR as determined by the ASTRO Phoenix definition of PSA nadir + 2 ng/mL.¹⁹ Another secondary objective was to determine changes in quality-of-life outcomes, and EPIC-26, PROMIS, and EQ-5D scores at enrollment and at 12 and 24 months. Time to PSA-CR and time BCR were defined from day 0 of the study, the initiation of ADT. Statistical significance was set at $P < .05$ for Kruskal-Wallis analysis of variance testing for quality of life and laboratory value comparisons. Data reporting and statistical analysis was done with STATA 16 (StataCorp) and Graphpad Prism.

Results

Patient characteristics

A flow diagram including enrollment and follow-up of the trial are summarized in Fig 2. Sixteen total patients were enrolled in the study between December 2015 and August 2020. Two patients were later found to not be eligible, and 3 withdrew before starting treatment. The baseline clinical and biological characteristics are presented in Table 1. Median age at enrollment was 69.0 years (interquartile range [IQR] 11.5). Six (54.5%), 2 (18.2%), and 1 (9.1%) patients were White, Black, and Asian, respectively. All patients had baseline Eastern Cooperative Oncology Group scores 0 to 1. Median body mass index was 26.7 (IQR 4.0). Eight (72.7%) patients had tumors T3 or higher,

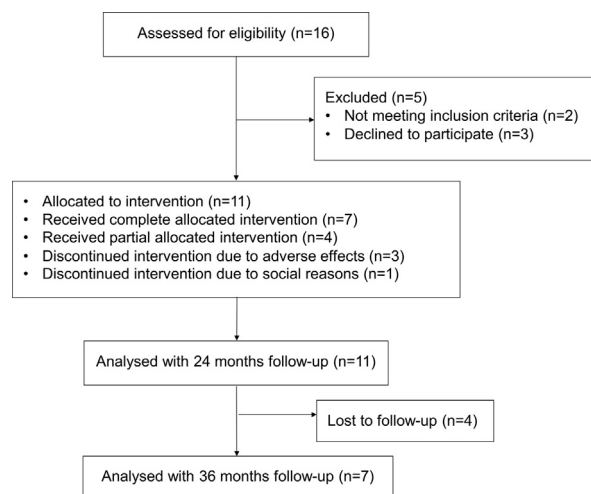


Fig. 2 Consolidated Standards of Reporting Trials (CONSORT) diagram of study design.

and 8 patients (72.7%) had N1 disease. Three (27.3%), 3 (27.3%), and 4 (36.4%) patients had Gleason grade 7, 8, and 9 disease, respectively. Median starting PSA and testosterone was 18.8 ng/mL (IQR 49.4) and 561 ng/dL (256), respectively. Median treatment duration was 24.0 months (IQR 11.9). Median follow-up time was 35.5 months (IQR 11.2), and 9 of 11 (81.8%) had protocol-defined follow-up completion of 36 months.

Clinical outcomes

Ten of 11 patients (90.9%) achieved PSA-CR at 120 days after initiation of ADT, with median time to PSA-CR of 4.20 months (IQR 0.83) and median nadir PSA was 0.015 ng/mL (IQR 0.015). All 11 patients achieved PSA-CR at completion of RT. Median time to testosterone < 50 ng/dL from initiation of ADT was 1.73 months (IQR 0.8), and median nadir testosterone was 18 ng/dL (IQR 6.5). PSA and testosterone laboratory measurements during follow-up period after completion of ADT, enzalutamide, and RT are summarized in Table 2. At 24 months of follow-up, 0 of 11 patients (0%) had BCR. Two patients were lost to follow-up between 24 and 36 months. At 36 months follow-up, 1 of 9 patients (11.1%) had BCR, with a time to BCR of 21.8 months. Of note, this patient discontinued therapy due to AE and did not complete the full 24 months of enzalutamide and leuproliide due to AEs.

Basic laboratory values at enrollment, 12 months, and 24 months follow-up are summarized in Table E1. There were no significant differences in levels of triglycerides, total cholesterol, high-density lipoprotein or low-density lipoprotein cholesterol, HgbA1c, blood glucose, creatinine, hemoglobin, or platelets at 12 or 24 months after treatment. AST, ALT, and White blood cell counts were

Table 1 Patient demographics and clinical characteristics

| | Baseline demographics and clinical characteristics at trial initiation |
|---|--|
| N | 11 |
| Median age (IQR) | 69.0 (11.5) |
| Race/ethnicity (%) | |
| Black | 2 (18.2%) |
| White | 6 (54.5%) |
| Asian | 1 (9.1%) |
| Hispanic/Latino | 0 (0%) |
| Unknown | 2 (18.2%) |
| ECOG (%) | |
| 0 | 9 (81.2%) |
| 1 | 2 (18.8%) |
| 2 | 0 (0%) |
| Median BMI (IQR) | 26.7 (4.0) |
| T Stage | |
| T2a | 1 (9.1%) |
| T2b | 1 (9.1%) |
| T2c | 1 (9.1%) |
| T3a | 2 (18.8%) |
| T3b | 6 (54.5%) |
| N stage | |
| N0 | 3 (27.3%) |
| N1 | 8 (72.7%) |
| Gleason grade | |
| 7 | 3 (27.3%) |
| 8 | 3 (27.3%) |
| 9 | 4 (36.4%) |
| Median starting PSA in ng/mL (IQR) | 18.8 (40.9) |
| Median starting testosterone in ng/dL (IQR) | 561 (223) |
| Median ADT treatment duration in months (IQR) | 24.0 (11.9) |
| Median follow-up duration in months (IQR) | 35.5 (11.2) |
| <i>Abbreviations:</i> BMI = body mass index; ECOG = Eastern Cooperative Oncology Group performance score; IQR = interquartile range; PSA = prostate specific antigen. | |

significantly lower after treatment ($P = .009$, $P = .001$, and $P = .01$, respectively).

Safety

All therapy-related AEs are summarized in Table 3. No grade 5 AEs were reported. One (9%) patient had grade 4

AE (seizure), and 4 (36.4%) patients had 6 total grade 3 AEs, including erectile dysfunction (2; 18.2%), myalgias (1; 9%), chronic kidney disease (1; 9%), anorexia (1; 9%), and hot flashes (1; 9%). Four patients (36.4%) stopped treatment early due to seizure, myalgias, hematuria, and social reasons. Of note, the seizure episode occurred 4 weeks after starting the study drug with negative workup including brain MRI; the findings were evaluated by a board-certified neurologist, who determined the event to be unlikely related to the study drug and discussed with the Institutional Review Board, who determined that continuation of the study was appropriate. Seven patients (62.6%) completed the 24-month therapeutic course. The most common minor (grade 1 or 2) AEs of the treatment regimen were hot flashes (11; 100%), urinary frequency (11; 100%), urinary urgency (11; 100%), and erectile dysfunction (8; 72.7%).

Quality of life outcomes

EPIC-26 scores at enrollment, and at 12- and 24-month follow-up are summarized in Table E2. No significant differences were reported in urinary or bowel measures or depression. There were significant decreases in reported sexual function outcomes, including ability to have an erection ($P = .0005$), ability to reach orgasm ($P = .0057$), quality of erections ($P = .037$), frequency of erections ($P = .0029$), and ability function sexually ($P = .0048$). There were significant increases in reported hot flashes ($P = .0015$), lack of energy ($P = .042$), and change in body weight ($P = .02$). Notably, the reported severity of sexual function, hot flashes, and lack of energy were improved at 24 months follow-up compared with 12 months, although these changes were not statistically significant.

PROMIS scores at enrollment, 12 and 24 months are summarized in Table E3. No significant differences were reported in all questions, including measures of physical function, anxiety, depression, fatigue, sleep disturbance, satisfaction with participation in social roles, and pain.

EQ-5D scores at enrollment, and at 12- and 24-months follow-up are summarized in Table E4. No significant differences were reported for mobility, self-care, usual activity, pain or discomfort, and anxiety or depression. Significant increases in overall health state were reported at 12 months and 24 months ($P = .0038$).

Discussion

The addition of ADT to definitive RT is a primary treatment modality for patients with high-risk localized PCa, as established by the landmark RTOG 85 to 31 and European Organisation For Research And Treatment Of Cancer (EORTC) 22863 trials demonstrating superiority

Table 2 PSA and testosterone values at follow-up

| N | Enrollment 11 | 6-8 wk 11 | 3-4 mo 11 | 6 mo 11 | 12 mo 11 | 18 mo 11 | 24 mo 11 | 36 mo 7 |
|---------------------------------------|------------------|--------------|---------------|---------------|---------------|---------------|-------------|-------------|
| Median PSA in ng/mL (IQR) | 18.8 (49.4) | 0.027 (0.52) | 0.015 (0.024) | 0.015 (0.038) | 0.015 (0.009) | 0.015 (0.044) | 0.1 (0.085) | 0.14 (0.34) |
| Median testosterone in ng/dL (IQR) | 561 (256) | 19 (7) | 19 (8) | 21 (10) | 20 (28) | 21 (27) | 147 (234) | 240 (474) |
| PSA-CR (%) | 100 | | | | | | | |
| BCR (%) | 0 | | 0 | 0 | 0 | 0 | 0 | 11.1 |

Abbreviations: BCR = biochemical recurrence; IQR = interquartile range; PSA = prostate specific antigen.

Table 3 Treatment related adverse events

| Adverse event (%) | Any grade | Grade 3 |
|---|-------------|-----------|
| Alopecia | 1 (9.1%) | 0 (0%) |
| Anorexia | 1 (9.1%) | 1 (9.1%) |
| Aspartate aminotransferase increased | 0 (0%) | 0 (0%) |
| Chronic kidney disease | 1 (9.1%) | 1 (9.1%) |
| Cognitive disturbance | 2 (18.2%) | 0 (0%) |
| Constipation | 1 (9.1%) | 0 (0%) |
| Creatinine increased | 1 (9.1%) | 0 (0%) |
| Cystitis noninfective | 2 (18.2%) | 0 (0%) |
| Diarrhea | 3 (27.3%) | 0 (0%) |
| Dysgeusia | 1 (9.1%) | 0 (0%) |
| Erectile dysfunction | 10 (90.9%) | 2 (18.2%) |
| Fatigue | 2 (18.2%) | 0 (0%) |
| Gastroesophageal reflux disease | 1 (9.1%) | 0 (0%) |
| Gastrointestinal disorders: Other | 1 (9.1%) | 0 (0%) |
| General disorders and administration site conditions: Other | 1 (9.1%) | 0 (0%) |
| Headache | 1 (9.1%) | 0 (0%) |
| Hot flashes | 11 (100.0%) | 1 (9.1%) |
| Libido decreased | 1 (9.1%) | 0 (0%) |
| Lightheadedness | 1 (9.1%) | 0 (0%) |
| Lymphedema | 2 (18.2%) | 0 (0%) |
| Musculoskeletal and connective tissue disorder: Other | 2 (18.2%) | 0 (0%) |
| Myalgia | 1 (9.1%) | 1 (9.1%) |
| Proctitis | 1 (9.1%) | 0 (0%) |
| Renal and urinary disorders: Other | 1 (9.1%) | 0 (0%) |
| Reproductive system and breast disorders: Other | 1 (9.1%) | 0 (0%) |
| Skin and subcutaneous tissue disorders: Other | 1 (9.1%) | 0 (0%) |
| Urinary frequency | 11 (100.0%) | 0 (0%) |
| Urinary incontinence | 3 (27.3%) | 0 (0%) |
| Urinary retention | 4 (36.4%) | 0 (0%) |
| Urinary tract infection | 1 (9.1%) | 0 (0%) |
| Urinary urgency | 11 (100.0%) | 0 (0%) |
| Weight gain | 3 (27.3%) | 0 (0%) |
| Total | 85 | 7 |

in terms of disease-free survival and overall survival of RT with ADT compared with RT alone.^{20,21} Similarly, for regional node-positive, nonmetastatic disease, retrospective analyses have also shown significantly higher rates of failure-free survival or OR in patients receiving definitive RT in addition to ADT.²²⁻²⁵ The duration of ADT treatment has been a subject of debate, but data from multiple studies including TROG 03.04 RADAR, RTOG 92 to 02, DART 01/05 GICOR, and EORTC 22961 showed improvements in overall survival with prolonged ADT of 18 to 36 months.²⁶⁻²⁹ The addition of an antiandrogen to a standard LHRH agonist has shown promise to further improve outcomes in high-risk PCa but has not been adequately addressed in clinical trials.

Enzalutamide was the first second-generation AR antagonist approved by the Food and Drug Administration and is now approved in combination with ADT for the treatment of castration resistant PCa, irrespective of the presence of metastases, pre- and postchemotherapy metastatic CRPC (mCPC), nonmetastatic CRPC (nmCPC), and as first-line therapy in mCSPC.³⁰ There is an increasing number of studies assessing the efficacy of enzalutamide in combination with current standard of care RT treatments. For example, Kaplan et al demonstrated effectiveness of enzalutamide monotherapy as a possible replacement for ADT in patients with intermediate PCa undergoing radiation therapy, using PSA response as a primary end point.³¹ Similarly, the STREAM and RTOG 3506 trials are currently evaluating enzalutamide in the salvage radiation setting in conjunction with ADT.^{26,32} Most recently, Attard et al in the phase 3 STAMPEDE trial show convincing evidence that addition of abiraterone with or without enzalutamide leads to improvement in metastasis-free and overall survival compared with ADT alone in high-risk PCa; although the addition of enzalutamide to abiraterone and ADT did not appear to provide additional treatment effect, the authors add the caveat that the study design could not exclude benefit of enzalutamide.³³ In this single arm, single site, phase 2 clinical trial, we demonstrate that combining nonsteroidal AR antagonist enzalutamide and leuprolide in patients undergoing definitive radiation therapy is reasonably well-tolerated and effective.

Most common side effects of the therapeutic regimen reported in this study include erectile dysfunction, myalgias, and hot flashes, which are all well-characterized toxicities of ADT.³⁴ In our study, the rate of grade 3 adverse events was 36%, which compares to 49% in the ENZAMET trial and 24.3% in the ARCHES trial, 2 commonly cited phase 3 randomized controlled trials of ADT and enzalutamide.^{35,36} Two patients terminated treatment due to ADT-related adverse effects, which is roughly in line with the 6% and 7.2% proportion of patients who terminated enzalutamide with ADT treatment in the ENZAMET and ARCHES trials, respectively.^{35,36} Urinary symptoms such as frequency and urgency were also

described in our cohort, known toxicities associated with pelvic radiation therapy.³⁷ One patient in the cohort developed seizures, subsequently leading to discontinuation of enzalutamide. Despite the negative workup and determination that the event to be unlikely related to the study drug, a direct relationship between the reported seizure and the study treatment cannot be excluded. Seizures are a known side effect of enzalutamide therapy, and has been identified as the most common adverse reaction leading to study treatment discontinuation with reported incidence of 0.6 to 0.9%.^{17,38} The UPWARD study recently showed that enzalutamide did not increase seizure incidence in men with pre-existing seizure risk factors, suggesting safety of use for PCa treatment in these cohorts.³⁹ Overall, the AE profiles of the addition of enzalutamide to ADT and RT were in line with a priori expectations; furthermore, at 12 months and 24 months of follow-up, patients demonstrated significant improvements in subjective reporting of their health state, further suggesting long-term tolerability of the treatment regimen.

Ten of 11 patients (91%) achieved PSA-CR at 120 days after initiation of ADT, which is favorable compared with the historic proportion of 70% from the RTOG 9413 trial.⁴⁰ All patients achieved PSA-CR, with median time to PSA-CR of 4.2 months, which aligns closely with the reported time to PSA-CR of 3.7 months from RTOG 9413. Response was sustained, with no BCR at 24 months follow-up in all 11 patients and 1 out of 9 patients with BCR at 36 months follow-up. Of note, this patient did not complete the full 24 months of enzalutamide and leuprolide due to AEs. These data are comparable to the reported 4-year BCR of more than 30% in the RTOG 9413 study in an equivalent cohort.⁴¹ Conclusions about efficacy of the combination in this study are limited by sample size, duration of follow-up and lack of a control group; larger clinical trials are thus required to definitively assess the relative clinical benefit of the combination therapy. One such clinical trial is the ENZARAD trial (NCT02446444), a phase 3 study investigating the addition of enzalutamide combined with ADT for patients with high-risk PCa undergoing primary radiation therapy, which has completed accrual and is anticipated to be completed between 2023 to 2024.

Conclusions

This trial suggests that combining nonsteroidal AR antagonist enzalutamide and leuprolide in patients undergoing definitive radiation therapy is reasonably well-tolerated and effective in achieving PSA complete response in high-risk localized or regional PCa. These results are promising, and future randomized controlled trials using larger patient cohorts with longer follow-up periods are thus warranted.

Supplementary materials

Supplementary material associated with this article can be found, in the online version at doi:10.1016/j.adro.2022.100941.

References

- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71:7–33.
- Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol.* 2010;28:1117–1123.
- D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA.* 1998;280:969–974.
- Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2019;17:479–505.
- Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2017;71:618–629.
- Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. *J Urol.* 2018;199:683–690.
- Zumsteg ZS, Zelefsky MJ, Woo KM, et al. Unification of favourable intermediate-, unfavourable intermediate-, and very high-risk stratification criteria for prostate cancer. *BJU Int.* 2017;120:E87–E95.
- Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: Final results of radiation therapy oncology group phase 3 randomized trial NRG oncology RTOG 9902. *Int J Radiat Oncol Biol Phys.* 2015;93:294–302.
- D'Amico AV, Xie W, McMahon E, et al. Radiation and androgen deprivation therapy with or without docetaxel in the management of nonmetastatic unfavourable-risk prostate cancer: A prospective randomized trial. *J Clin Oncol.* 2021;JCO2100596.
- Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: The randomized phase III NRG Oncology RTOG 0521 Trial. *J Clin Oncol.* 2019;37:1159–1168.
- Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med.* 1989;321:419–424.
- James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med.* 2017;377:338–351.
- 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.
- Ardiani A, Farsaci B, Rogers CJ, et al. Combination therapy with a second-generation androgen receptor antagonist and a metastasis vaccine improves survival in a spontaneous prostate cancer model. *Clin Cancer Res.* 2013;19:6205–6218.
- 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.
- Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014;371:1755–1756.
- Tombal B, Borre M, Rathenborg P, et al. Enzalutamide monotherapy in hormone-naïve prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. *Lancet Oncol.* 2014;15:592–600.
- Tombal B, Borre M, Rathenborg P, et al. Long-term efficacy and safety of enzalutamide monotherapy in hormone-naïve prostate cancer: 1- and 2-year open-label follow-up results. *Eur Urol.* 2015;68:787–794.
- Roach 3rd M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer. *Recommendations of the RTOG-ASTRO Phoenix Consensus Conference.* 2006;65:965–974.
- Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol.* 2010;11:1066–1073.
- Briganti A, Wiegel T, Joniau S, et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: Results of a match-controlled multi-institutional analysis. *Eur Urol.* 2012;62:472–487.
- Lin CC, Gray PJ, Jemal A, Efstathiou JA. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. *J Natl Cancer Inst.* 2015:107.
- Tward JD, Kokeny KE, Shrieve DC. Radiation therapy for clinically node-positive prostate adenocarcinoma is correlated with improved overall and prostate cancer-specific survival. *Pract Radiat Oncol.* 2013;3:234–240.
- Rusthoven CG, Carlson JA, Waxweiler TV, et al. The impact of definitive local therapy for lymph node-positive prostate cancer: A population-based study. *Int J Radiat Oncol Biol Phys.* 2014;88:1064–1073.
- James ND, Spears MR, Clarke NW, et al. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: Data from patients in the control arm of the STAMPEDE Trial. *JAMA Oncol.* 2016;2:348–357.
- Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. *Lancet Oncol.* 2019;20:267–281.
- Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: A phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol.* 2008;26:2497–2504.
- Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): A randomised, controlled, phase 3 trial. *Lancet Oncol.* 2015;16:320–327.
- Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma: Long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys.* 2005;61:1285–1290.
- Laccetti AL, Morris MJ, Kantoff PW. A clinical evaluation of enzalutamide in metastatic castration-sensitive prostate cancer: Guiding principles for treatment selection and perspectives on research. *Onco Targets Ther.* 2020;13:13247–13263.
- Bubley GJ, Kaplan I, Bhatt R, et al. Phase II study of enzalutamide with radiation therapy for intermediate risk prostate cancer: A phase 2 study. *Int J Radiat Oncol Biol Phys.* 2021;110:1416–1422.
- Bitting RL, Healy P, George DJ, et al. Phase II trial of enzalutamide and androgen deprivation therapy with salvage radiation in men with high-risk prostate-specific antigen recurrent prostate cancer: The STREAM Trial. *Eur Urol Oncol.* 2021;4:948–954.
- Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk nonmetastatic prostate cancer: A meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet.* 2022;399:447–460.

34. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol*. 2015;67:825–836.
35. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37:2974–2986.
36. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med*. 2019;381:121–131.
37. Elliott SP, Malaeb BS. Long-term urinary adverse effects of pelvic radiotherapy. *World J Urol*. 2011;29:35–41.
38. Ning YM, Pierce W, Maher VE, et al. Enzalutamide for treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res*. 2013;19:6067–6073.
39. Slovin S, Clark W, Carles J, et al. Seizure rates in enzalutamide-treated men with metastatic castration-resistant prostate cancer and risk of seizure: The UPWARD study. *JAMA Oncol*. 2018;4:702–706.
40. Cury FL, Hunt D, Roach 3rd M, et al. Prostate-specific antigen response after short-term hormone therapy plus external-beam radiotherapy and outcome in patients treated on Radiation Therapy Oncology Group study 9413. *Cancer*. 2013;119:1999–2004.
41. Roach 3rd M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: Long-term results of RTOG 8610. *J Clin Oncol*. 2008;26:585–591.