Title

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Journal

European Urology, 85(6)

Authors

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Publication Date

2024-06-01

DOI

10.1016/j.eururo.2024.01.021

Peer reviewed

HHS Public Access

Author manuscript

Eur Urol. Author manuscript; available in PMC 2024 September 10.

Published in final edited form as:

Eur Urol. 2024 June ; 85(6): 517–520. doi:10.1016/j.eururo.2024.01.021.

Systemic and Tumor-directed Therapy for Oligorecurrent Metastatic Prostate Cancer (SATURN): Primary Endpoint Results from a Phase 2 Clinical Trial

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Associate Editor: Gianluca Giannarini

Author contributions: Amar U. Kishan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kishan, Nickols.

Acquisition of data: Nikitas, Sachdeva, Kishan.

Analysis and interpretation of data: Nikitas, Kishan, Nickols.

Drafting of the manuscript: Nikitas, Kishan, Nickols.

Critical revision of the manuscript for important intellectual content: Nikitas, Rettig, Shen, Reiter, Lee, Steinberg, Valle, Sachdeva, Romero, Calais, Czernin, Nickols, Kishan.

Statistical analysis: Nikitas, Romero, Kishan, Nickols.

Obtaining funding: Kishan.

Administrative, technical, or material support: Kishan.

Supervision: Kishan, Nickols.

Other: None.

Financial disclosures: Amar U. Kishan certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Amar U. Kishan has received personal fees from Varian Medical Systems and Boston Scientific; speaking honoraria, consulting fees, and research support from Janssen and Varian Medical Systems; and grants from Janssen and Lantheus outside the submitted work. Matthew Rettig has received speaking honoraria or consulting fees from Ambrx, Amgen, Clovis Oncology, Roivant, NKimmune, Johnson & Johnson, and Bayer outside the submitted work. Robert Reiter has received speaking honoraria from Janssen Oncology, Genomic Health, ImaginAb, Bayer Schering Pharma, and Pfizer outside the submitted work. Nicholas G. Nickols has received grants from Janssen, Lantheus, and Bayer, and personal fees from PrimeFour outside the submitted work. Michael L. Steinberg has received consulting fees from ViewRay outside the submitted work. Jeremie Calais reports prior consulting services for Advanced Accelerator Applications, Astellas, Blue Earth Diagnostics, Curium Pharma, DS Pharma, EXINI, GE Healthcare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Lightpoint Medical, Lantheus, Monrol, Novartis, Progenics, POINT Biopharma, Radiomedix, Sanofi, and Telix Pharmaceuticals outside of the submitted work. The remaining authors have nothing to disclose.

Peer Review Summary and Supplementary data

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.01.021.

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Abstract

Nearly all men with metastatic hormone-sensitive prostate cancer treated with intermittent androgen deprivation therapy (ADT) experience recurrence within 6 mo of testosterone recovery. We conducted a single-arm phase 2 trial to evaluate whether addition of dual androgen receptor pathway inhibitors (ARPIs) and metastasis-directed stereotactic body radiotherapy (SBRT) to intermittent ADT improves recurrence rates for men with between one and five nonvisceral, extrapelvic metastases on prostate-specific membrane antigen positron emission tomography/computed tomography after prior radical prostatectomy. Patients received 6 mo of androgen annihilation therapy (AAT; leuprolide, abiraterone acetate plus prednisone, and apalutamide) and metastasis-directed SBRT. The primary endpoint was the percentage of patients with prostate-specific antigen (PSA) <0.05 ng/ml 6 mo after testosterone recovery (≥150 ng/dl), with the study powered to detect an improvement from 1% to 12%. We enrolled 28 men between March 2021 and June 2022. Median follow-up was 20 mo (interquartile range 16–22). Twenty-six patients (93%) completed SBRT with 6 mo of hormone therapy, of whom six discontinued at least one ARPI; two patients withdrew prematurely. At 6 mo after testosterone recovery, PSA was maintained at <0.05 ng/ml in 13/26 patients (50%, 95% confidence interval 32–67%). Rates of grade 2 and 3 AAT toxicity were 21% and 21%. The results confirm that addition of metastasis-directed SBRT to highly potent systemic therapy can maintain low PSA after testosterone recovery, although further studies are needed to clarify the optimal systemic therapy regimen.

Patient summary: We tested a combination of intensified hormone therapy (called androgen annihilation therapy) and radiotherapy targeted at metastases in men with recurrence of metastatic prostate cancer. We found that half of patients were recurrence-free 6 months after their testosterone level recovered, and that less than a quarter of patients experienced a severe drug-related side effect. Overall, this appears to be an effective therapy with acceptable side effects.

This trial is registered on ClinicalTrials.gov as NCT03902951.

Keywords

Abiraterone acetate; Androgen annihilation therapy; Apalutamide; Leuprolide; Metastasis-directed therapy; Oligorecurrence; Prostate cancer; Stereotactic body radiotherapy

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Intermittent androgen deprivation therapy (ADT) offers better quality of life in comparison to continuous ADT for men with metastatic hormone-sensitive prostate cancer (mHSPC) [1]. Unfortunately, nearly all men in this setting experience recurrence within 6 mo of testosterone recovery.

For oligometastatic prostate cancer (≤5 metastases), a combination of intermittent ADT and metastasis-directed radiotherapy can significantly improve progression-free survival (PFS) [2,3]. Refinement of targeting using prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) imaging to guide metastasis-directed therapy may further improve PFS [4].

In parallel with these efforts in oligometastatic disease, multiple studies have shown that addition of an androgen receptor pathway inhibitor (ARPI) to ADT significantly improves survival for men with mHSPC [5,6]. Androgen annihilation therapy (AAT), achieved by combining ADT with dual ARPIs (apalutamide and abiraterone acetate plus prednisone), leads to more profound inhibition of androgen receptor signaling and significantly improves radiographic PFS in comparison to ADT plus a single ARPI for men with metastatic castration-resistant prostate cancer (CPRC) [7]. Unfortunately, long-course AAT is associated with grade ≥3 toxicity rates of 60% [8].

In the SATURN trial (NCT03902951), we hypothesized that integration of short-course AAT with PSMA PET/CT–guided, metastasis-directed stereotactic body radiotherapy (SBRT) would significantly improve PFS for men with oligorecurrent mHSPC after radical prostatectomy. This was a prospective, single-center, single-arm phase 2 study that enrolled men with recurrence following radical prostatectomy involving one to five lesions on PSMA PET/CT that would be classified as M1a–b according to American Joint Committee on Cancer 8th edition criteria.

Patients were treated with leuprolide (1-mo or 3-mo depot injections), apalutamide (240 mg daily), and abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) for 6 mo. At 1 mo after AAT initiation, SBRT was delivered to all metastatic sites over one, three, or five fractions, with or without prostate-bed radiotherapy. Prostate-specific antigen (PSA) and testosterone were checked every 30 d following AAT for the first 6 mo, and every 3 mo thereafter.

The primary endpoint was the percentage of patients achieving PSA <0.05 ng/ml 6 mo after their serum testosterone recovered (≥150 ng/dl) following AAT. This was reported with a 95% confidence interval (CI) calculated using a z test. The study had >80% power to test the null hypothesis of 1% (recurrence in virtually all patients with intermittent ADT alone) versus the study hypothesis of 12% using the exact binomial test ($\alpha = 0.05$). A pilot study of radical prostatectomy, ADT, and metastasis-directed SBRT for de novo oligometastatic HSPC showed a eugonadal PSA control rate of 20% [7], so a lower 12% rate was estimated for oligorecurrent mHSPC. Secondary endpoints included PFS and eugonadal PFS. Progression was defined as PSA ≥0.05 ng/ml. PFS was calculated from the time of AAT initiation using the Kaplan-Meier method. Patients were censored at last follow-up. For patients whose testosterone recovered, eugonadal PFS was calculated from the time of testosterone recovery using the Kaplan-Meier method. Patients with progression before testosterone recovery were counted as progressing at time 0. Adverse events were graded according to Common Terminology Criteria for Adverse Events v4.0. Further details can be found in the Supplementary material.

Between March 2021 and June 2022, 28 patients enrolled in the study. Twelve patients (43%) had two or more lesions (Table 1). Median PSA at enrollment was 2.6 ng/ml (interquartile range [IQR] 1.0–7.7). The median lesion size was 1.0 cm (IQR 0.7–1.2). Median follow-up was 20 mo (IQR 16–22).

Twenty-six patients (93%) completed metastasis-directed SBRT with 6 mo of hormone therapy: 20 completed ADT with dual ARPIs, five completed ADT with a single ARPI, and one completed ADT monotherapy (Supplementary Fig. 1). Two patients (7.1%) withdrew prematurely because of adverse effects.

At 6 mo after testosterone recovery, PSA was maintained at <0.05 ng/ml in 13/26 patients (50%, 95% CI 32–67%). Median PFS was 19.3 mo (95% CI 12.8–25.7; Fig. 1). The PFS rate was 69% (95% CI 51–87%) at 1 yr and 36% (95% CI 13–59%) at 2 yr.

Among 13 patients with PSA progression, eight developed PSMA-avid metastatic disease at a median of 16.1 mo (IQR 14.4–18.0) from AAT initiation. Six were retreated at a median of 17.8 mo (IQR 15.5–19.5) from AAT initiation. One (3.8%) developed CRPC. There were no deaths. Details regarding the PSMA PET/CT response, multivariable analysis, and eugonadal PFS are provided in the Supplementary material.

Six patients (21%) each experienced grade 2 and grade 3 toxicity from AAT (Supplementary Table 1). Two patients (7.7%) experienced grade 2 toxicity and no patients experienced grade 3 toxicity from SBRT.

To the best of our knowledge, SATURN is the first trial to integrate short-course AAT with PSMA PET/CT–guided, metastasis-directed SBRT in men with oligorecurrent mHSPC. This approach was well tolerated, and 90% of men completed therapy with at least one ARPI. The rate of grade 3 toxicity was 21%, which compares favorably to the 60% reported for long-course AAT and 33% reported for longterm ADT monotherapy [8,9]. At 6 mo after testosterone recovery, 50% of patients remained recurrence-free, with median eugonadal PFS of 11.4 mo. According to multivariable analysis, patients with no prior hormonal therapy were less likely to experience recurrence. Taken together, the results show that short-term AAT with metastasis-directed SBRT appears to offer a substantial disease-free interval following testosterone recovery.

These results build on the recently reported EXTEND trial [3]. In EXTEND, men with prostate cancer who had up to five metastases (including N1 disease) according to conventional imaging or fluciclovine PET/CT were randomized to intermittent ADT with or without metastasis-directed radiotherapy. Addition of metastasis-directed radiotherapy was associated with significantly higher PFS and eugonadal PFS. In comparison to EXTEND, SATURN only included men with extrapelvic disease, used a lower threshold for defining PSA progression, and treated patients with a shorter duration of systemic therapy, potentially explaining the lower PFS (11.4 mo vs 19.3 mo in EXTEND). Furthermore, SATURN exclusively used PSMA PET/CT–defined targets, which may be biologically distinct from conventional imaging–defined targets [10]. Overall, both trials support the integration of metastasis-directed radiotherapy with shorter-course systemic therapy.

Our study has several important limitations. First, the sample size was modest. Second, the patient population was heterogeneous, with significant variation in the number of metastatic sites, prior recurrences, and prior hormone therapy. We have yet to identify the ideal population for this treatment regimen. Third, there was no independent central reading of PSMA PET/CT scans. Fourth, this was not a randomized study.

In conclusion, short-course AAT plus SBRT was well tolerated and achieved durable disease control in half of men with PSMA PET/CT-identified oligorecurrent M1a–b disease. These findings will inform future studies evaluating whether the optimal systemic therapy regimen with metastasis-directed SBRT in this setting is dual-agent ARPI with ADT, ADT with single-agent ARPI, or perhaps even single-agent ARPI alone.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding/Support and role of the sponsor:

This study was an investigator-sponsored trial, supported by the Jonsson Comprehensive Cancer Center in collaboration with Janssen Scientific Affairs, LLC. Dr. Kishan discloses research support from grant P50CA09213 from the Prostate Cancer National Institutes of Health Specialized Programs of Research Excellence and grant PC210066 from the Department of Defense.

Dr. Nikitas discloses researh support from the Christiaan W. Schiepers Theranostics Fellowship award.

Data sharing statement:

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

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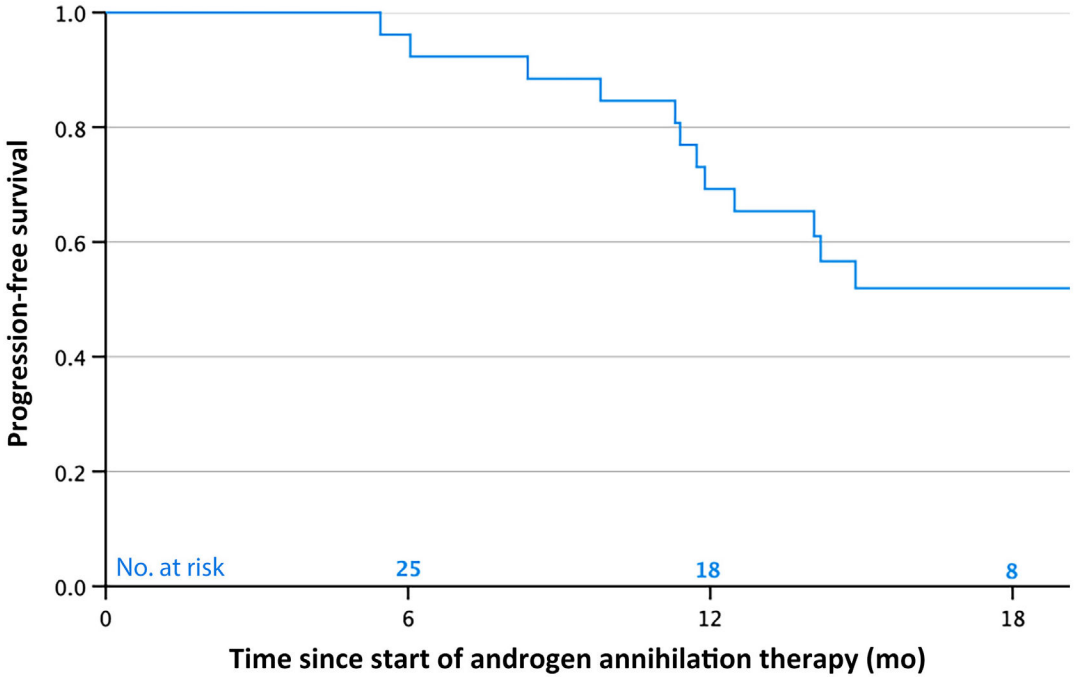

Fig. 1 –.

Progression-free survival from initiation of androgen annihilation therapy (n = 26 patients) according to Kaplan-Meier analysis. The number of patients at risk is shown for each time point.

Table 1 –

Patient and treatment characteristics

Parameter	Result
Characteristics at baseline (28 patients)	
Median age at enrollment, yr (IQR)	70.9 (66.3–76.5)
Initial ISUP grade group, *n* (%)	
2	5 (18)
3	9 (32)
4	3 (11)
5	10 (36)
Unknown	1 (3.6)
Initial pathological stage, *n* (%)	
pT2 N0 M0	9 (32)
pT3–4 N0 M0	11 (39)
pT3 N1 M0	4 (14)
pT3 N0 M1	2 (7.1)
Unknown	2 (7.1)
Median time since initial diagnosis, yr (IQR)	5.1 (2.7–9.0)
Prior therapies, *n* (%)	
RP ± ADT/ARPI	9 (32)
RP + salvage RT ± ADT/ARPI	9 (32)
RP + salvage RT + MDT ± ADT/ARPI	4 (14)
RP + salvage RT + ADT/ARPI + chemotherapy	1 (3.6)
RP + MDT ± ADT/ARPI	2 (7.1)
Neoadjuvant RT + RP ± ADT/ARPI	3 (11)
Median number of prior recurrences (IQR)	1 (0–1)
Median PSA at enrollment, ng/ml (IQR)	2.6 (1.0–7.7)
Median PSA doubling time, mo (IQR)	4.4 (1.8–7.7)
Median number of lesions on PSMA PET/CT (IQR)	1 (1–2)
Staging on PSMA PET/CT, *n* (%)	
N0 M1a	7 (25)
N1 M1a	5 (18)
N0 M1b	13 (46)
N1 M1b	3 (11)
Lesion data (46 lesions)	
Location of lesions on PSMA PET/CT, *n* (%)	
Prostate bed	4 (8.7)
Bone	18 (39)
Lymph nodes	24 (52)
Median size of PSMA-avid lesions, cm (IQR)	1.0 (0.7–1.2)
Median SUVmax for PSMA-avid lesions (IQR)	6.9 (3.2–14.6)
SBRT data (41 SBRT plans)	

Parameter	Result
SBRT fractionation plan, *n* (%)	
18–20 Gy in 1 fraction	3 (7.3)
30 Gy in 3 fractions	8 (20)
30 Gy in 5 fractions	10 (24)
35–40 Gy in 5 fractions	20 (49)
Further SBRT details (26 patients)	
Prostate bed inclusion, *n* (%)	4 (15)
Elective pelvic lymph-node irradiation, *n* (%)	2 (7.7)

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; IQR = interquartile range; ISUP = International Society of Urological Pathology; MDT = metastasis-directed therapy; PSMA PET/ CT = prostate-specific membrane antigen positron emission tomography/ computed tomography; SBRT = stereotactic body radiotherapy; SUVmax = maximum standardized uptake value.