Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic Castrate-Resistant Prostate Cancer: A Randomized Phase II Trial (ARTO)

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ABSTRACT

PURPOSE ARTO (ClinicalTrials.gov identifier: NCT03449719) is a multicenter, phase II randomized clinical trial testing the benefit of adding stereotactic body radiation therapy (SBRT) to abiraterone acetate and prednisone (AAP) in patients with oligometastatic castrate-resistant prostate cancer (CRPC).

MATERIALS AND METHODS All patients were affected by oligometastatic CRPC as defined as three or less nonvisceral metastatic lesions. Patients were randomly assigned 1:1 to receive either AAP alone (control arm) or AAP with concomitant SBRT to all the sites of disease (experimental arm). Primary end point was the rate of biochemical response (BR), defined as a prostate-specific antigen (PSA) decrease ≥50% from baseline measured at 6 months from treatment start. Complete BR (CBR), defined as PSA < 0.2 ng/mL at 6 months from treatment, and progression-free survival (PFS) were secondary end points.

RESULTS One hundred and fifty-seven patients were enrolled between January 2019 and September 2022. BR was detected in 79.6% of patients (92% *v* 68.3% in the experimental *v* control arm, respectively), with an odds ratio (OR) of 5.34 (95% CI, 2.05 to 13.88; $P = .001$) in favor of the experimental arm. CBR was detected in 38.8% of patients (56% *v* 23.2% in the experimental *v* control arm, respectively), with an OR of 4.22 (95% CI, 2.12 to 8.38; $P < .001$). SBRT yielded a significant PFS improvement, with a hazard ratio for progression of 0.35 (95% CI, 0.21 to 0.57; $P < .001$) in the experimental versus control arm.

CONCLUSION The trial reached its primary end point of biochemical control and PFS, suggesting a clinical advantage for SBRT in addition to first-line AAP treatment in patients with metastatic castration-resistant prostate cancer.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC) include different systemic agents. Both taxane chemotherapy[1] and androgen receptor–targeted agents (ARTA) improved overall survival (OS) when compared with placebo.[2,3] However, a limited number of metastatic lesions may indicate an intermediate status of disease, characterized by a lower tumor burden, which was defined as oligometastatic disease for the first time by Hellman and Weichselbaum[4] in 1995. This disease status persists also in some patients developing mCRPC, suggesting that a well-selected cohort of patients may benefit from local treatment of metastatic sites in addition to the best practice of systemic therapy. There is level I evidence that similar treatment strategies improve outcomes in patients with distinct histology (eg, melanoma, lung, colorectal, and prostate).[5] A significant benefit of metastasis-directed therapy (MDT) was reported by two randomized trials that included only metastatic hormone-sensitive prostate cancer (HSPC).[6,7] Moreover, the benefit of this treatment strategy was confirmed in a pooled analysis of these two trials.[8] Stereotactic body radiation therapy (SBRT) represents a noninvasive therapeutic strategy for the treatment of oligometastatic disease. Despite several retrospective reports about its use in mCRPC,[9,10] currently limited prospective evidence exists on a combined approach of SBRT with ARTA in patients with mCRPC. Zhang et al published a phase II trial including 89 patients with oligometastatic CRPC (oligo-mCRPC) treated on 128 lesions identified by

CONTEXT

Key Objective

Does stereotactic body radiation therapy (SBRT) provide any additional benefit to standard systemic treatment in men with oligometastatic disease and undergoing first-line metastatic castration-resistant prostate cancer treatment?

Knowledge Generated

ARTO (ClinicalTrials.gov identifier: NCT03449719) trial suggests that patients treated with concomitant SBRT and abiraterone acetate may have significant advantage in terms of prostate-specific antigen (PSA) reduction at 6 months and progression-free survival when compared with patients treated with standard systemic treatment alone. These results were obtained without any meaningful signal of increased rate of adverse event.

Relevance *(M.A. Carducci)*

Targeting these sites of disease with SBRT and standard of care agents is safe and feasible, with evolving data from studies like this showing consistency in the benefits to this approach in enhancing response rates measured by PSA as well as lengthening time to radiographic progression. These results should be confirmed in larger studies and placed into context with the changing landscape of treatment options for metastatic hormone sensitive and metastatic castration resistant disease.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD.

choline-positron emission tomography (PET), with a median OS of 29.3 months and prostate-specific antigen (PSA) progression-free survival (PFS) of 40% and 21% at 1 and 2 years, respectively. Treatment was considered safe, with no grade 3 adverse events (AEs) recorded.[11] ICE-PAC was another phase II trial testing SBRT associated with avelumab in CRPC setting. Overall, results showed radiologic PFS and OS of 8.4 and 14.1 months, respectively.[12]

To our knowledge, here, we report for the first time the results of the primary and secondary end points of the ARTO trial (ClinicalTrials.gov identifier: NCT03449719), a multicenter randomized phase II clinical trial, exploring the synergistic effect of SBRT and abiraterone acetate with prednisone (AAP) in a cohort of patients affected by oligo-mCRPC.

The main focus of the trial is to evaluate the synergistic effect of SBRT and AAP in a well-selected cohort of men with oligo-mCRPC.

MATERIALS AND METHODS

Study Design

ARTO (ClinicalTrials.gov identifier: NCT03449719) is a randomized phase II trial designed to assess the benefit of SBRT in addition to AAP as first-line therapy for patients with oligo-mCRPC. All patients had to have mCRPC with three or fewer bone or nodal metastatic lesions. Sixteen Italian centers participated in the trial and actively enrolled patients on a competitive basis. Conventional imaging (computed tomography [CT] and/or bone scan) or PET-CT with choline, fluciclovine, or prostate-specific membrane antigen (PSMA) staging was allowed according to physician choice when CRPC was suspected. No previous systemic treatments for mCRPC were allowed. Patients with visceral lesions (eg, lung or liver) were excluded. Patients were randomly assigned 1:1 to receive standard systemic treatment with androgen-deprivation therapy (ADT) with AAP (control arm) or standard treatment plus SBRT to all sites of metastatic disease (experimental arm). The Protocol (online only) was approved by the Ethical Committee of Area Vasta Centro (approval no. 12855_spe, October 9, 2018). The study was performed according to the Declaration of Helsinki principles. Informed consent to participate in the study was obtained from each enrolled patient.

Treatment Procedures

AAP was administered in both arms at 1,000 mg once daily plus prednisone 5 mg orally twice daily. ADT with luteinizing hormone–releasing hormone analog was concomitantly administered. In the treatment arm, all SBRT doses and fractionations were allowed provided that treatment was administered to all sites of disease with a biologically effective dose of at least 100 Gy using an alpha/beta ratio of three for prostate cancer.[13] SBRT planning technique was according to physician choice, provided that American Association of Physicists in Medicine report and constraints were used.[14] To evaluate PSA response at comparable end points from treatment start in the two arms, all patients in the treatment arm underwent SBRT at 30 days (±3 days) from the date of first AAP administration.

Assessments

Patients were followed every 3 months with PSA and complete hematologic blood tests. Restaging was performed in case of clinical or biochemical progression according to Prostate Cancer Working Group 3 criteria.[15] Restaging was performed using the same baseline imaging methods chosen for initial assessment. Safety and dosing compliance were evaluated during each study visit or at treatment discontinuation if applicable. AEs were collected and reported according to Common Terminology Criteria for Adverse events (version 4.03).

End Points

The difference between the two arms in terms of biochemical response (BR) rate (defined as percentage of patients with a PSA decrease ≥50% compared with baseline) at 6 months after AAP treatment start was the primary end point of the trial. The secondary end points included complete BR (CBR) rate (defined as percentage of patients with PSA ≤ 0.2 ng/mL at 6 months after AAP treatment start); PFS, defined as a composite end point including time between AAP treatment start and radiologic or biochemical progression, start of following treatment, or death (whichever occurred first); and OS, defined as the time between AAP treatment start and death.

Randomization and Sample Size

Patients were randomly assigned in a 1:1 ratio using a computer-generated random number table. Patients were stratified by random permuted blocks according to center, performance status (0-1 *v* >1), and number of metastases (1 *v* >1). Assuming a proportion of patients achieving BR in control arm of 62%,[16] 156 patients were required to show an absolute improvement of 20% in the experimental arm with a 5% type 1 error rate and a statistical power of 80%. Considering a 10% rate of dropout during follow-up, the final sample size initially calculated was 174 patients (87 for each arm). However, after 4 years, because of slow accrual and the absence of dropout, the institutional review board decided to stop the recruitment at 157 patients. Because of logistical reasons, patients and investigators were aware of the experimental arm.

Statistical Analysis

The distribution of categorical and continuous variables was compared between the control and the treatment arms by means of Fisher's exact and Wilcoxon's rank sum tests, respectively. The effect of the arm allocation (experimental *v* control) and baseline covariates (baseline PSA for each increase by 1 ng/mL, the number of metastatic sites 1 *v* >1, restaging at enrollment with PSMA/fluciclovine PET *v* every other method, presence of bone metastasis *v* nodal only disease, and de novo metastatic *v* metachronous disease) on the odds of achieving BR or CBR was investigated by means of logistic regression models. All tests were conducted in an intention-to-treat analysis. Kaplan-Meier analysis was performed and log-rank test was used to compare survival in experimental versus control arm. Hazard ratios (HRs) and corresponding 95% CIs were calculated by Cox regression analysis.

RESULTS

Demographic

Between January 2019 and September 2022, 157 patients enrolled in the trial. Seventy-five and 82 patients were assigned to the experimental arm and the control arm, respectively. All patients received their allocated treatment except for one patient in the treatment arm in whom SBRT was not administered because of patient's refusal (Fig 1). All patients completed at least 6 months of follow-up to report primary end point analysis. Baseline population features were well balanced between the two arms (Table 1). The dose and fractionation schedules used in the SBRT arm are reported in Appendix Table A1 (online only).

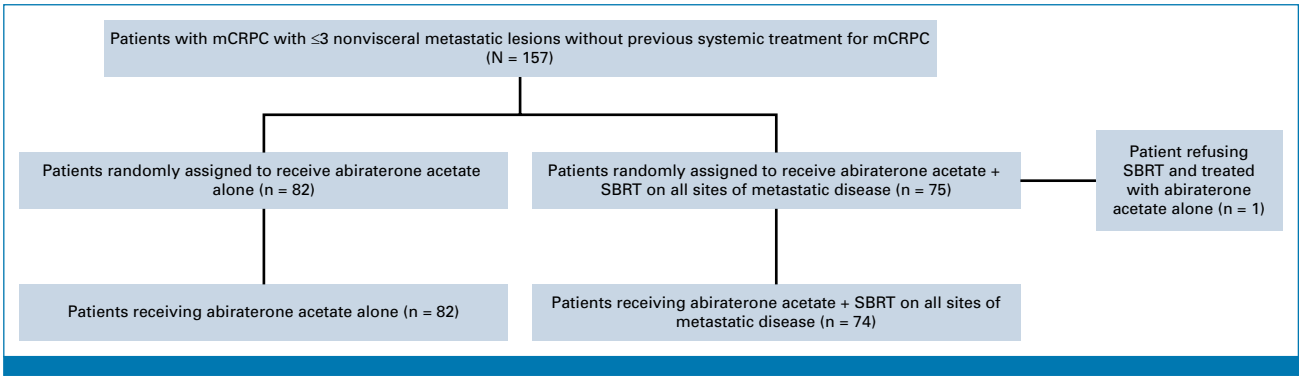

FIG 1. Flow diagram summarizing enrollment and treatment allocation. mCRPC, metastatic castration-resistant prostate cancer; SBRT, stereotactic body radiation therapy.

TABLE 1. Baseline Population Features

Characteristic	AAP (n = 82)	AAP + SBRT (n = 75)	*P*
Age, years, median (IQR)	74 (68-79)	74 (68-79)	.61
ISUP grade, No. (%)			.87
≤3	15 (18.3)	13 (17.3)	
>3	67 (81.7)	62 (82.7)	
Lesion, No. (%)			.05
1	25 (30.5)	34 (45.4)	
>1	57 (69.5)	41 (54.6)	
Metastatic sites, No. (%)			.22
Nodal only	44 (53.6)	33 (44)	
Bone	38 (46.4)	42 (56)	
Staging, No. (%)			.12
Conventional	11 (13.4)	4 (5.3)	
Choline PET	54 (65.9)	48 (64)	
PSMA/fluciclovine PET	17 (20.7)	23 (30.7)	
Baseline PSA, median (IQR)	3.42 (1.46-9.35)	3.42 (1.47-9.36)	.14

Abbreviations: AAP, abiraterone acetate and prednisone; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiation therapy.

Biochemical Response

BR was detected in 79.6% of patients (92% *v* 68.3% in experimental *v* control arm, respectively), with an odds ratio (OR) for BR of 5.34 (95% CI, 2.05 to 13.88; $P = .001$) in favor of the experimental arm. On univariate analysis, only treatment and baseline PSA were significantly associated with rate of BR, while there was no significant impact from the number of metastatic sites (1 *v* >1), staging method (PSMA/fluciclovine *v* every other), presence of bone metastases, or the presence of de novo metastatic disease. On multivariate analysis, only treatment persisted as an independent predictive factor of BR, with an OR of 4.50 (95% CI, 1.7 to 11.95; $P = .003$; Table 2).

Complete Biochemical Response

The CBR was detected in 38.8% of patients (56% *v* 23.2% in experimental *v* control arm, respectively), with an OR of 4.22 (95% CI, 2.12 to 8.38; $P < .001$). On univariate analysis, only treatment arm and staging method (PSMA/fluciclovine *v* every other) had a significant impact on CBR, while no impact of the other factors was detected. Treatment arm persisted as the only independent predictive factor of CBR at multivariate analysis, with an OR of 3.64 (95% CI, 1.80 to 7.38; $P < .001$; Table 3).

Survival

After a median follow-up of 24.9 months (IQR, 17.1-35.8), 75 patients had progression (22 *v* 53 in the experimental *v* control arm, respectively). Median PFS was not reached versus 17 months in the experimental versus control arm, respectively. SBRT yielded significant improvement in terms of PFS, with a HR for progression of 0.35 (95% CI, 0.21 to 0.57) in favor of the AAP + SBRT arm ($P < .001$). Biochemical progression was reported as the first PFS event in 36 patients (11 and 25 in experimental *v* control arm, respectively), while

TABLE 2. Univariate and Multivariate Analyses for Biochemical Response According to Predefined Predictive Factors

	Univariate Analysis				Multivariate Analysis			
Factor	OR	Lower CI	Higher CI	*P*	OR	Lower CI	Higher CI	*P*
AAP + SBRT *v* AAP	5.34	2.05	13.88	**.001**	4.50	1.70	11.95	**.003**
Basal PSA	0.98	0.95	1.00	**.042**	0.10	0.96	1.01	.122
Metastatic sites, No. (>1 *v* 1)	0.44	0.18	1.05	.065	—	—	—	—
Staging at enrollment (PSMA/fluciclovine *v* others)	1.03	0.42	2.53	.945	—	—	—	—
Presence of bone metastases (yes *v* no)	0.77	0.35	1.67	.503	—	—	—	—
Presence of de novo metastatic disease (yes *v* no)	1.15	0.35	3.73	.816	—	—	—	—

NOTE. Bold indicates significant *P* values.
Abbreviations: AAP, abiraterone acetate and prednisone; OR, odds ratio; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiation therapy.

TABLE 3. Univariate and Multivariate Analyses for Complete Biochemical Response According to Predefined Predictive Factors

	Univariate Analysis				Multivariate Analysis			
Factor	OR	Lower CI	Higher CI	*P*	OR	Lower CI	Higher CI	*P*
AAP + SBRT *v* AAP	4.22	2.12	8.38	**<.001**	3.64	1.80	7.38	**<.001**
Basal PSA	0.94	0.89	0.99	**.018**	0.95	0.91	1.00	.074
Metastatic sites, No. (>1 *v* 1)	0.81	0.42	1.55	.522	—	—	—	—
Staging at enrollment (PSMA/fluciclovine *v* others)	2.13	1.03	4.41	**.042**	1.64	0.74	3.59	.220
Presence of bone metastases (yes *v* no)	1.37	0.72	2.61	.340	—	—	—	—
Presence of de novo metastatic disease (yes *v* no)	0.66	0.25	1.73	.394	—	—	—	—

NOTE. Bold indicates significant *P* values.
Abbreviations: AAP, abiraterone acetate and prednisone; OR, odds ratio; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiation therapy.

radiologic progression was reported as the first PFS event in 39 patients (11 and 28 in experimental *v* control arm, respectively). Chi-square test showed that biochemical and radiologic PFS events were well balanced across trial arms ($P = .82$). Median biochemical and radiologic PFS were not reached versus 36 months and not reached versus 34 months in the experimental versus control arm, respectively. Significant benefit in terms of biochemical PFS (HR, 0.33 [95% CI, 0.16 to 0.67]; $P = 0.002$) and radiologic PFS (HR, 0.39 [95% CI, 0.19 to 0.81]; $P = 0.011$) was detected in the experimental arm (Appendix Figs A1 and A2). After progression, subsequent treatment consisted of second-line systemic therapy, SBRT for oligoprogressive disease, or best supportive care for poor clinical conditions in 40, 22, and 12 patients, respectively. Median time between AAP start and subsequent treatment approach was 36 versus 18 months in the experimental versus control arm, respectively. SBRT in experimental arm provided a significant benefit in terms of freedom from additional treatment approach (HR, 0.37 [95% CI, 0.22 to 0.61]; $P < .001$; Appendix Fig A3). Twenty-four patients died (9 *v* 15 in the experimental *v* control arm, respectively). Median OS was not reached in both arms of treatment. HR for death was 0.65 (95% CI, 0.28 to 1.49) with a nonsignificant trend in favor of the experimental versus control arm (Figs 2A and 2B).

Safety

Overall, G1/G2 AEs were reported in 48 (64%) and 54 (65.8%) of patients in the experimental versus control arm, respectively; grade >2 AEs occurred in 8 (10.6%) and 13 (15.8%) of patients in the experimental versus control arm, respectively. A summary of AEs is reported in Table 4. Most toxicities (ie, blood count and other blood test abnormalities, fatigue, hot flashes, and hyperglycemia) were mild and related to systemic treatment. Cardiovascular disorders were recorded in 10 (13.3%) and 14 (17%) patients in the experimental versus control arm, respectively. Osteoporosis/fractures, hematuria, and gastrointestinal disorders (including proctitis, enteritis, or rectal hemorrhage) were considered AEs that were potentially related to SBRT. Of these, osteoporosis or fracture was recorded in two (2.7%) and five (6%) patients, hematuria occurred in four (4.9%) and four (5.3%), and gastrointestinal disorders were reported in two (2.7%) and one (1.2%) patient in the experimental and control arm, respectively.

DISCUSSION

To date, to our knowledge, ARTO (ClinicalTrials.gov identifier: NCT03449719) is the first randomized prospective clinical trial to report the outcome in patients with oligo-mCRPC undergoing first -line systemic treatment alone or with SBRT. The results show that the addition of SBRT to first-line AAP treatment yielded a significant increase in 6-month BR and CBR. A significant benefit in PFS was detected in favor of the combined regimen. Interestingly, the benefit in terms of radiologic PFS and freedom from needing additional treatment confirmed the ability of SBRT to prevent the development of new distant metastases and extend the duration of first-line AAP in the experimental arm. Median follow-up was long enough to suggest that these results are reliable and deserve attention, especially considering their magnitude (HR, 0.35 in favor of the experimental arm). Of note, median PFS in the control arm was 17 months, which is similar to that reported in the AAP arm of the COU AA 302 trial (16.5 months).[3] These findings suggest that the enrolled population were representative of patients previously studied and PFS advantage could be related to the SBRT effect rather than selection bias. No OS advantage was reported, but after 23 months of follow-up, these data may require more time to mature, especially given the good prognosis of the population studied (oligometastatic patients without visceral metastases). Moreover, no relevant toxicity events were detected for concomitant administration of SBRT, especially AEs such as fractures, hematuria, or gastrointestinal disorders. These side effects were potentially related to SBRT and were expected to be relevant in the experimental arm. Current prospective data about use of SBRT in mCRPC setting are limited to two single-arm prospective phase II trials.[11,12] Several retrospective studies confirmed the clinical feasibility of this

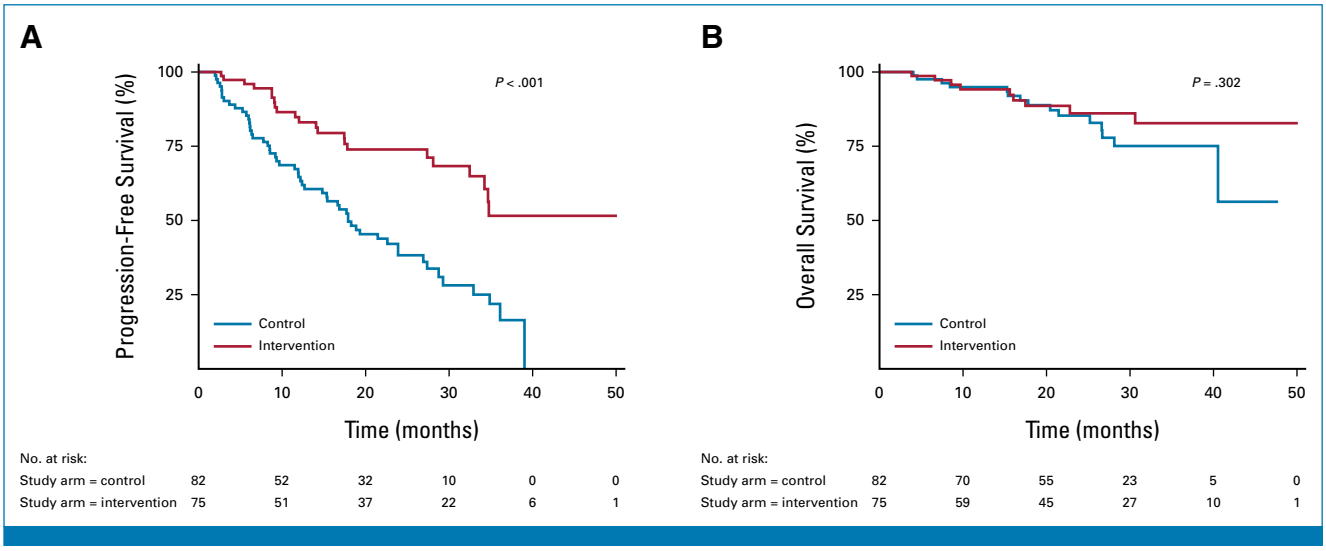

FIG 2. Cox regression analysis for (A) progression-free survival and (B) overall survival in the experimental versus control arm.

approach in routine clinical practice.[17] However, these populations are not comparable to patients enrolled in the ARTO trial. Indeed, patients in these reports underwent SBRT in different and often more advanced settings compared with the present cohort, which is characterized by upfront oligo mCRPC treatment with first-line AAP. The precise timing for SBRT in addition to standard systemic treatment (eg, administered upfront *v* later in case of oligoprogressive disease) is an important issue. Considering the potential role of SBRT as ablative treatment for metastatic foci harboring clonogens resistant to castration,[18] we advocate the early use of this treatment strategy in the natural course of disease. In our opinion, this approach may maximize the synergistic effects of SBRT and ARTA treatment in the mCRPC. Conversely, waiting until the onset of oligoprogressive disease during systemic treatment may lead to the development of multiple polyclonal seedings, reducing the impact of local treatment on patients' prognosis. The main limitations of the current trial are related to its primary end point and the heterogeneous staging modalities used at the time of enrollment. Other recent phase II trials explored similar end points (eg, BR) to test efficacy of radiation-based treatments in patients with mCRPC.[19] Moreover, this end point helped to maintain the sample size appropriate for a randomized phase II design. Regarding the staging issue, conventional imaging (eg, CT and bone scan) is currently considered the standard to assess patients with CRPC.[20] However, next-generation imaging may increase the detection rate of systemic spread and it is more helpful to provide early and extensive MDT in patients with CRPC.[21] Potential advantage

TABLE 4. Adverse Events Reported in Experimental and Control Arms

	AAP, No. (%)		AAP + SBRT, No. (%)	
Type of Adverse Event	G1/2	G > 2	G1/2	G > 2
Blood count abnormalities	4 (4.9)	1 (1.2)	6 (8)	1 (1.3)
Other blood test abnormalities	13 (15.8)	4 (4.9)	10 (13.3)	1 (1.3)
Osteoporosis/Fracture	5 (6)	0 (0)	2 (2.7)	0 (0)
Fatigue	8 (9.7)	1 (1.2)	9 (12)	0 (0)
Hot flashes	2 (2.4)	0 (0)	2 (2.7)	0 (0)
Hyperglicemia/diabetes	3 (3.6)	0 (0)	3 (4)	0 (0)
Lower urinary tract symptoms	4 (4.9)	3 (3.6)	2 (2.7)	1 (1.3)
Hematuria	3 (3.6)	1 (1.2)	2 (2.7)	2 (2.7)
Gastrointestinal disorders	1 (1.2)	0 (0)	2 (2.7)	0 (0)
Cardiovascular disorders	11 (13.4)	3 (3.6)	7 (9.3)	3 (4)
Limb edema	0 (0)	0 (0)	3 (4)	0
Total	54 (65.8)	13 (15.8)	48 (64)	8 (10.6)

Abbreviations: AAP, abiraterone acetate and prednisone; SBRT, stereotactic body radiation therapy.

of a mixed cohort of patients staged with different imaging methods include the possibility to explore whether an earlier and more extensive local approach may improve the benefit of SBRT. PSMA/fluciclovine restaging at enrollment was selected as a baseline covariate in the logistic regression models. Data from the present analysis suggest that the treatment of all PSMA/fluciclovine-avid metastases had no impact on response to treatment itself compared with other baseline imaging, but this was related to an unplanned post hoc analysis of ARTO trial and should be taken with caution. Of note, use of fluciclovine PET was very uncommon within ARTO trial and involved only four patients overall (two for each arm of treatment). Another potential limitation could be related to the slight imbalance in terms of number of lesions (1 *v* >1) reported in favor of the treatment arm. This could be considered as a possible confounding variable, given borderline statistical significance of the difference.

Several ongoing trials are investigating the role of SBRT + ARTA in this scenario: DECREASE (ClinicalTrials.gov identifier: NCT04319783), FORCE (ClinicalTrials.gov identifier: NCT03556904), OLI-CR-PC (ClinicalTrials.gov identifier: NCT04141709), PCS IX (ClinicalTrials.gov identifier: NCT02685397), and PILLAR (ClinicalTrials.gov identifier: NCT03503344). Overall, these trials will constitute the ground basis for integrating local and systemic treatment in mCRPC, testing the addition of SBRT to apalutamide, enzalutamide, or darolutamide. It should be noted that the treatment of mCRPC is a rapidly evolving landscape, especially given promising reports about use of poly-(adenosine diphosphate–ribose) polymerase and AAP in patients with first-line mCRPC,[22,23] and the introduction of ARTA treatment in metastatic hormone-sensitive disease.[24-26] Interestingly, only patients with first-line mCRPC could be included in the ARTO trial, but previous intensified therapy in HSPC scenario was allowed. However, only seven patients underwent treatment intensification before abiraterone therapy (two patients received previous docetaxel in control arm, and four and one patients received previous docetaxel and apalutamide in experimental arm, respectively). For this reason, implementation of SBRT in this scenario could be an evolving paradigm, and prospective trials testing different combinations are eagerly needed to provide clinical rationale for SBRT use in oligometastatic prostate cancer. PERSIAN trial (ClinicalTrials.gov identifier: NCT05717660) is a brand-new multicenter randomized phase II clinical trial enrolling patients with oligometastatic HSPC randomly assigned to receive either ADT + apalutamide versus ADT + apalutamide + SBRT on all distant metastases. The trial started its enrollment on March 2023 and the end of accrual is planned for 2025.

In conclusion, the ARTO (ClinicalTrials.gov identifier: NCT03449719) trial reached its primary end point and showed a significant improvement in terms of BR rate in the AAP + SBRT arm. SBRT yielded significant improvement in terms of PFS, suggesting a safe clinical advantage for SBRT in addition to first-line AAP treatment for patients with mCRPC. Phase III trials are warranted to test survival end points in larger cohorts.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Stereotactic Body Radiation Therapy and Abiraterone Acetate for Patients Affected by Oligometastatic Castrate-Resistant Prostate Cancer: A Randomized Phase II Trial (ARTO)

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No other potential conflicts of interest were reported.

APPENDIX 1. ARTO WORKING GROUP

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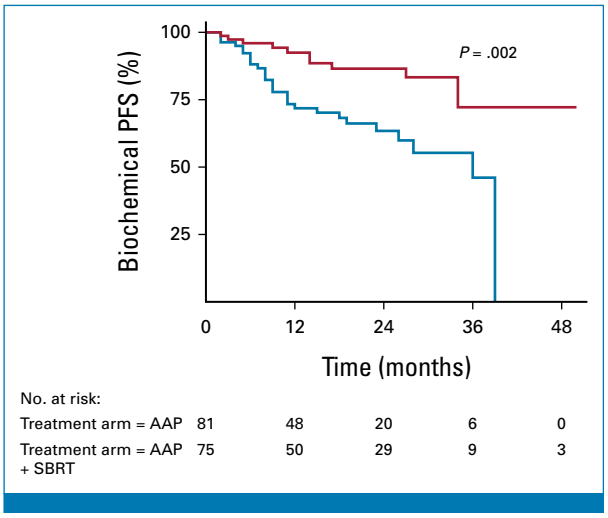

FIG A1. Cox regression analysis for biochemical PFS in the experimental versus control arm. AAP, abiraterone acetate and prednisone; PFS, progression-free survival; SBRT, stereotactic body radiation therapy.

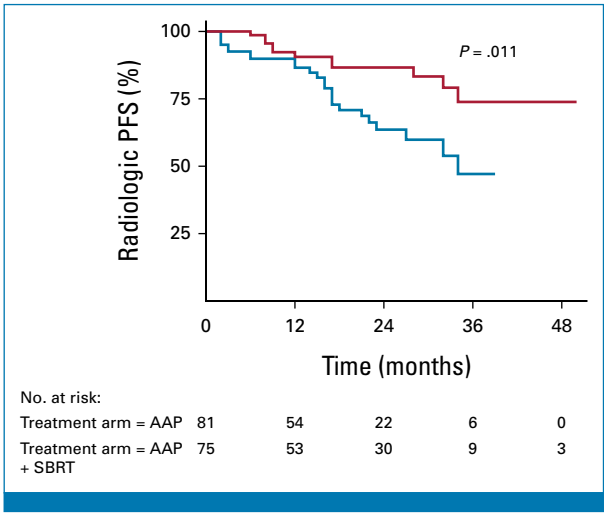

FIG A2. Cox regression analysis for radiologic PFS in the experimental versus control arm. AAP, abiraterone acetate and prednisone; PFS, progression-free survival; SBRT, stereotactic body radiation therapy.

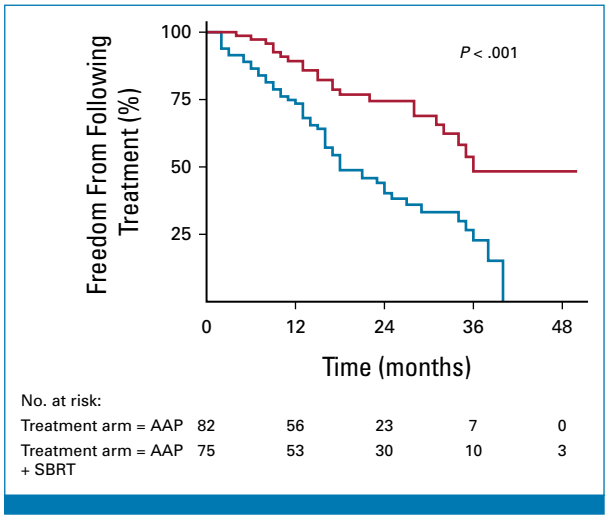

FIG A3. Cox regression analysis for freedom from following treatment approach in the experimental versus control arm. AAP, abiraterone acetate and prednisone; SBRT, stereotactic body radiation therapy.

TABLE A1. Dose/Fractionation Schedules Used for All Patients Randomly Assigned to Experimental Arm

Dose/Fractionation Schedule (Gy/Fractions)	BED_3	Patients, No.
16/1	101.3	2
32.5/5	102.9	9
27/3	108	14
35/5	116.7	22
30/3	130	16
40/5	146.7	6
36/3	180	6

Abbreviation: BED, biologically effective dose.