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Original Research

A phase 2 randomized clinical trial of abiraterone plus ADT, apalutamide, or abiraterone and apalutamide in patients with advanced prostate cancer with non-castrate testosterone levels (LACOG 0415)

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Abstract ***Background:*** Androgen deprivation therapy (ADT) combined with apalutamide, abiraterone acetate plus prednisone, enzalutamide, or docetaxel are the standard treatments for advanced castration-sensitive prostate cancer (CSPC). We investigated ADT-free alternatives for advanced CSPC.

Patients and methods: LACOG 0415 is a phase 2, open-label, non-comparative, randomized trial. Patients with advanced CSPC were randomized (1:1:1) to receive goserelin plus abiraterone acetate and prednisone (ADT plus AAP arm), apalutamide (APA arm), or apalutamide plus abiraterone acetate and prednisone (APA plus AAP arm). The primary endpoint was the proportion of patients with PSA of ≤0.2 ng/mL at week 25 in the modified intention-to-treat population. Safety analyses were performed in all patients with at least one dose of the study drug.

Results: Of 128 randomized patients, 120 patients were evaluable for PSA response at week 25; 17.2% had a high-risk biochemical recurrence, 8.6% had locally advanced disease, and 74.2% had distant metastases. At week 25, PSA of ≤0.2 ng/mL was observed in 75.6% (95%CI 59.7%–87.6%), 60.0% (95%CI 43.3%–75.1%), and 79.5% (95%CI 63.5%–90.7%) of patients in ADT plus AAP, APA, and APA plus AAP arms, respectively. PSA decline of ≥80% was observed in 100%, 90.0%, and 97.4%, respectively. Grade 3–4 AEs were observed in 31.0%, 21.4% and 36.4%, respectively. Testosterone levels increased significantly in the APA arm and decreased significantly in ADT plus AAP and APA plus AAP arms.

Conclusions: ADT-free alternatives provide a high PSA response in advanced CSPC, although the APA arm did not reach the expected rate of PSA of ≤0.2 ng/mL at week 25. These results warrant further investigation of ADT-free treatments as alternatives in advanced CSPC.

Source study registration: ClinicalTrials.gov NCT02867020.

1. Introduction

Androgen deprivation therapy (ADT) is considered the cornerstone of advanced prostate cancer treatment, either with bilateral orchiectomy or GnRH agonist/antagonist [1]. Despite the high response rates with this strategy, ADT is associated with well-known adverse events (AEs) [2,3].

Early generation non-steroidal antiandrogen monotherapy compared to ADT was associated with inferior overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (CSPC), despite a favourable and distinct safety profile [4–6]. Conversely, androgen signalling inhibitors (ASI) – abiraterone, enzalutamide and apalutamide – and docetaxel combined with ADT have been shown to improve OS and other clinical outcomes when compared to ADT alone in CSPC [7–11]. As a result, patients are being exposed to ADT for longer periods, which in turn can lead to treatment-related adverse events (TRAEs) that may impact health-related quality of life (HRQoL) [12]. There is limited evidence for the clinical application of these ASI as monotherapy in advanced CSPC. A phase II trial, including 67 hormone-naive prostate cancer (15% with metastatic disease) patients for whom hormone therapy was indicated and who had non-castration levels of testosterone, evaluated the efficacy of enzalutamide 160 mg/day and showed PSA decline of 80% or greater at week 25 in 92.5% of patients [13]. In addition, single-agent ASI in combination with ADT have a favourable safety profile in castration-resistant prostate cancer (CRPC) [14,15], and there are ongoing trials evaluating ASI in combination with ADT in the CSPC setting. On the other hand, it is important to emphasize that in chemotherapy-naïve metastatic CRPC patients, the combination of ADT with abiraterone and apalutamide had greater toxicity than the combination of ADT with abiraterone [16].

We hypothesized that ADT-free alternatives with ASI could provide high efficacy with an acceptable safety profile and HRQoL in patients with advanced CSPC.

2. Patients and methods

LACOG 0415 is a phase 2, open-label, non-comparative, randomized trial evaluating the efficacy of ADT plus AAP versus APA alone versus APA plus AAP, at standard doses, in patients with advanced CSPC. The trial was designed and led by the genitourinary steering committee from the Latin American Cooperative Oncology Group and conducted in 14 Brazilian sites.

The study protocol was approved by the Institutional Review Board of all participating institutions and was conducted in accordance with the current International Conference on Harmonization guidelines for Good Clinical Practice and according to the Declaration of Helsinki. Written informed consent was obtained from

all participants by investigators before any study procedure. This trial was registered in ClinicalTrials.gov (NCT02867020).

The study included patients with: (1) locally advanced prostate cancer with positive lymph nodes, not candidates to radical surgery or radiotherapy and PSA of ≥2 ng/mL; (2) high-risk biochemical recurrence defined as PSA of ≥4 ng/mL and PSA doubling-time <10 months, or PSA of ≥20 ng/mL; or (3) metastatic CSPC and PSA of ≥2 ng/mL. All included patients had testosterone levels ≥230 ng/dL at baseline. Patients were excluded if they had received prior ADT except in the context of local therapy with an ADT-free interval of ≥12months prior to study entry. The full protocol is available as Supplementary Material.

Patients were randomized (1:1:1) to receive: ADT plus AAP arm - subcutaneous goserelin (10.8 mg every 12 weeks) plus abiraterone acetate 1000 mg (4 × 250 mg tablets daily) and prednisone 5 mg twice daily; APA arm – apalutamide 240 mg (4 × 60 mg tablets daily) alone without ADT; and APA plus AAP arm – apalutamide 240 mg (4 × 60 mg tablets daily) plus abiraterone acetate 1000 mg (4 × 250 mg tablets daily) and prednisone 5 mg twice daily without ADT. Randomization was balanced by using randomly permuted blocks and was done across all study sites using a centralized Interactive Web Response System. Subjects were stratified by performance status (ECOG 0–1 versus 2) and metastatic disease (yes vs. no).

Per protocol, study treatment was planned until week 25. Patients were treated until week 25, disease progression (radiographic per RECIST 1.1 and/or symptomatic ± biochemical progression according to the Prostate Cancer Working Group Criteria 3), unacceptable toxicity or consent withdrawal. Patients who benefited from the study treatment were allowed to continue beyond week 25 (extension phase) at the investigator discretion.

The primary endpoint was the proportion of patients who achieved PSA level of ≤0.2 ng/mL at week 25 in each of the three arms, based on its value as a surrogate endpoint for long term outcomes in previous studies [17,18]. The study was non-comparative, and therefore formal statistical comparisons among the three arms were not performed. Secondary endpoints were PSA decline of ≥50% and ≥80% at week 25; maximum PSA decline and overall PSA change from baseline up to week 25 and up to week 52; radiographic progression-free survival (rPFS) at week 25; testosterone levels during treatment; safety profile; HRQoL assessed by FACT-P, and PSA progression [19].

Patients were required to have adequate haematological, metabolic, and cardiac functional status. Physical examination, haematological and metabolic panel, PSA and circulating testosterone levels were assessed at screening, on day 1, and every 4 weeks until week 25. An additional PSA confirmatory test was performed at week 28. Testosterone levels were assessed by chemiluminescence assay locally at each site laboratory. HRQoL assessments were performed at baseline and every 4 weeks until week 25. CT scans were performed at baseline and week 25. Blood samples and paraffin-embedded tumour tissue samples were collected and stored for future translational research analyses.

The sample size using Fleming one-stage method was based on the proportion of patients with PSA of ≤0.2 ng/mL at week 25. With a sample size of 114 participants (38 per arm), the study would have 80% power to reject a PSA of ≤0.2 ng/mL at week 25 rate of 45% or less at a 5% significance level, with an expected PSA of ≤0.2 ng/mL at week 25 rate for each treatment arm of about 65%. Allowing a 10% dropout, we planned to enrol 126 participants.

PSA response analyses were performed in a modified intention-to-treat (mITT) population, which includes all randomized patients who had PSA information both at baseline and week 25. An additional sensitivity analysis was performed for the primary endpoint, including all randomized patients, whereas missing PSA data at week 25 were labelled as failures. All safety analyses were done on all patients who had taken at least one dose of the study drug. No interim analysis for futility was planned. All statistical analyses specified in this protocol were conducted using SAS v.9.4.

3. Results

At 14 sites, 190 patients were screened from October-2017 to April-2019; 128 were randomized. Forty-two patients were assigned to ADT plus AAP arm, 42 to APA arm, and 44 to APA plus AAP arm (Supplementary Material Fig. 1).

The baseline demographics and disease characteristics were well balanced and described in Table 1. Of note, metastatic disease was present in 74.2%, while 17.2% had high-risk biochemical recurrence disease only, and 8.6% had locally advanced disease.

3.1. Primary endpoint

The results presented are based on the clinical cutoff date of 12th November, 2019, with a median follow-up of 14 months. A total of 120 patients were evaluable for the primary endpoint: 41 patients in ADT plus AAP arm, 40 patients in APA arm, and 39 patients in APA plus AAP arm. The proportion of patients who achieved PSA of ≤0.2 ng/mL at week 25 was 75.6% (95% CI 59.7%–87.6%) in ADT plus AAP arm, 60.0% (95% CI 43.3%–75.1%) in APA arm, and 79.5% (95% CI 63.5%–90.7%) in APA plus AAP arm (Table 2). ADT plus AAP arm and APA plus AAP arm reached the prespecified 65% rate of PSA of ≤0.2 ng/mL at week 25; APA arm failed to reach that threshold. Eight patients who

Table 1
Baseline characteristics.

Characteristic	ADT plus AAP (N = 42)	APA (N = 42)	APA plus AAP (N = 44)	Total (N = 128)
Median age, yr (range)	69 (51–85)	69.5 (53–88)	71 (49–87)	70 (49–88)
Median duration of prostate cancer, yr (range)	1 (0–18)	0.5 (0–11)	0 (0–21)	0 (0–21)
Median PSA, ng/mL (IQR)	16.7 (6.4–50.0)	19.9 (7.2–68.5)	32.4 (7.1–141.5)	22.5 (6.9–117.4)
Median testosterone, ng/dL (IQR)	424.7 (331–469.1)	434.5 (360–532.9)	413 (312.4–518)	420.7 (334.1–508.9)
ECOG 0–1[a], *n* (%)	41 (97.6)	42 (100)	44 (100)	127 (99.2)
Characteristics at initial diagnosis				
Total Gleason Score, *n* (%)				
≤6	3 (7.1)	2 (4.8)	5 (11.4)	10 (7.8)
7	18 (42.9)	17 (40.5)	10 (22.7)	45 (35.2)
≥8	21 (50.0)	23 (54.7)	29 (65.9)	73 (57.0)
Clinical tumour stage, primary tumour[b], *n* (%)				
T0-T2	15 (35.7)	15 (35.7)	22 (50.0)	52 (40.6)
T3	23 (54.8)	21 (50.0)	14 (31.8)	58 (45.3)
T4	3 (7.1)	3 (7.1)	7 (15.9)	13 (10.2)
Unknown	1 (2.4)	3 (7.1)	1 (2.3)	5 (3.9)
Clinical lymph node stage, *n* (%)				
N0	17 (40.5)	18 (42.9)	16 (36.4)	51 (39.8)
N1	17 (40.5)	16 (38.1)	18 (40.9)	51 (39.8)
Nx or unknown	8 (19.0)	8 (19.0)	10 (22.7)	26 (20.4)
Distant metastases, *n* (%)				
M0	20 (47.6)	17 (40.5)	17 (38.6)	54 (42.2)
M1	19 (45.2)	21 (50.0)	23 (52.3)	63 (46.2)
Mx or unknown	3 (7.1)	4 (9.5)	4 (9.1)	11 (8.6)
Disease status at study entry				
Criteria for ADT indication, *n* (%)				
Biochemical recurrence	7 (16.7)	8 (19.0)	7 (15.9)	22 (17.2)
Locally advanced disease	6 (14.3)	2 (4.8)	3 (6.8)	11 (8.6)
Metastatic disease	29 (69.0)	32 (76.2)	34 (77.3)	95 (74.2)
Previous interventions, *n* (%)				
Radiotherapy	17 (40.5)	16 (38.1)	14 (31.8)	47 (36.7)
Prostatectomy	20 (47.6)	18 (42.9)	17 (38.6)	55 (43.0)
(Neo)Adjuvant Androgen Deprivation Therapy	4 (9.5)	6 (14.3)	4 (9.1)	14 (10.9)

PSA = prostate-specific antigen. ADT = androgen deprivation therapy. IQR = interquartile range.
[a] Scores for the Eastern Cooperative Oncology Group (ECOG) performance status are assessed on a 5-point scale.
[b] Tumour stage was assessed according to the 2009 tumour–node–metastasis (TNM) classification, 7th edition.

Table 2
Primary and secondary endpoints at week 25 in the mITT population.

	ADT plus AAP (N = 41)	APA (N = 40)	APA plus AAP (N = 39)
Primary endpoint, *n* (%)			
PSA ≤0.2 ng/mL	31 (75.6)	24 (60.0)	31 (79.5)
Secondary endpoints, *n* (%)			
PSA decline ≥50%	41 (100)	37 (92.5)	39 (100)
PSA decline ≥80%	41 (100)	36 (90.0)	39 (97.4)
Mean change in testosterone levels from baseline to week 25, % (SD)	−97.4 (31.8)	134.3 (110.6)	−73.8 (65.1)
Median Testosterone Level, ng/dL (IQR)			
Baseline	424.7 (331–469.1)	434.5 (360–532.9)	413 (312.4–518)
Week 4	9.0 (2.4–12)	983 (796–1200)	37.9 (9.9–133)
Week 8	9.0 (2.5–11.2)	1034.6 (806–1219)	49 (15–103)
Week 12	9.0 (2.4–12)	1060.9 (738–1239)	44.7 (12–155)
Week 16	8.9 (2.5–10)	1060 (794.8–1258.4)	25.5 (9–108)
Week 20	9.0 (2.5–12)	1034.9 (769–1235.5)	37.2 (9–87.7)
Week 25	9.0 (3.6–12) (N = 32)	1022 (723–1260) (N = 35)	30.4 (9–139) (N = 35)
Radiographic progression *, *n* (%)	1 (3.1)	1 (2.9)	0

PSA = prostate-specific antigen. IQR = interquartile range. SD = standard deviation. * Patients without evaluable images at week 25 or with overall response unable to assess were excluded.

discontinued treatment before week 25 and did not have PSA available at week 25 were not included in mITT analysis. Sensitivity analysis was performed to adjust for those missing PSA values at week 25, considering them as failures, and similar findings were observed with PSA of ≤0.2 ng/mL at week 25 in 73.8% (95% CI 58.0%–86.1%), 57.1% (95% CI 41.0%–72.3%), and 70.5% (95% CI 54.8%–83.2%), respectively. Sub-group analyses according to the metastatic status at baseline were performed. Patients without the metastatic disease had a higher proportion of PSA of ≤0.2 ng/mL at week 25 with 92.3%, 80.0% and 87.5%, respectively. Patients with metastatic disease had a slightly lower proportion with 67.9%, 53.3% and 77.4%, respectively.

3.2. Secondary endpoints

3.2.1. Efficacy

The PSA decline of ≥50% and ≥80% at week 25 were observed in the vast majority of patients in all three arms, as described in Table 2. Fig. 1 represents the Waterfall plot for patient maximum PSA decline from baseline up to week 25 for each treatment arm. Of note, PSA progression at week 25 was only observed in three patients in the APA arm, all of whom had metastatic disease at baseline. In addition, another three patients had clinical progression (one in each arm); two also had radiographic progression (one patient in ADT plus AAP arm and the other in APA arm). The three patients with clinical progression all had metastatic disease at baseline (two with bone metastases and one with visceral disease). No death events were reported (Table 2). Analyses of median radiographic PFS and OS are immature.

3.2.2. Testosterone pharmacodynamics

Regarding another secondary endpoint, the proportion of patients with testosterone level <50 ng/dL (castration level) at week 25 was 97.5% (n = 40) in ADT plus AAP arm and 64% (n = 25) in APA plus AAP arms. All patients in the APA arm had testosterone levels >50 ng/dL. Mean testosterone levels had a clinically significant increase from baseline in the APA arm and a clinically significant decrease in ADT plus AAP and APA plus AAP arms (Table 2). Fig. 2 shows the median testosterone levels for each treatment arm from baseline through week 25.

3.2.3. Safety

AEs of any cause occurred in 92.9% of patients in ADT plus AAP arm, 92.9% in APA arm, and 95.5% in APA plus AAP arm. Grade 3–4 AEs were 31.0%, 21.4% and 36.4%, respectively (Table 3). TRAEs of all grades were observed in 71.4% in ADT plus AAP arm, 81.0% in APA arm, and 81.8% in APA plus AAP arm. Grade 3–4 TRAEs were 19.0%, 16.7% and 22.7%, respectively.

All-grade gynaecomastia (55%) and breast pain (14%) were more common in APA arm. All-grade hypertension, hyperglycemia and hot flushes happened more frequently in ADT plus AAP (21%, 10% and 38%, respectively) and APA plus AAP (20%, 11% and 30%, respectively) arms. All-grade rash and pruritus were more common in APA (26% and 17%, respectively) and APA plus AAP (18% and 14%, respectively) arms (Table 3). Treatment interruptions due to toxicity occurred in 4.8%, 9.5% and 18.2% patients from ADT plus AAP, APA, and APA plus AAP arms, respectively. Dose reductions were required for abiraterone in two patients in ADT plus AAP arm. Nine patients discontinued therapy before week 25, six of them due to toxicity (ADT plus AAP arm: one with stroke; APA arm: one with grade 3 rash; APA plus AAP arm: one with grade 3 rash and acute renal failure, one with grade 3 hypertension, one with grade 3 rash/pruritus and one with grade 3 pruritus).

Overall mean FACT-P score remained consistent over 25 weeks of treatment within each treatment arm. Also, there was no significant difference among the three treatment arms during the study period (Supplementary Material Fig. 2).

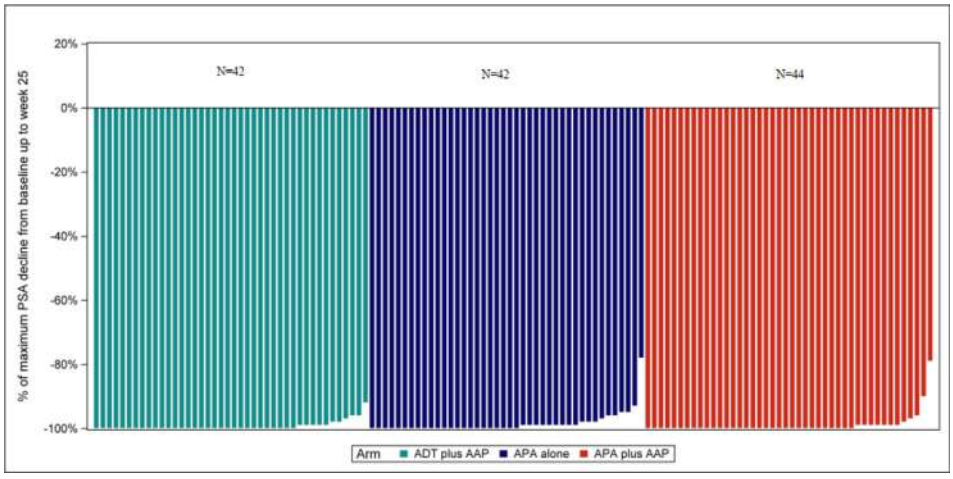

Fig. 1. **Waterfall plot maximum PSA decline from baseline up to week 25 (intention-to-treat).** PSA = prostate-specific antigen.

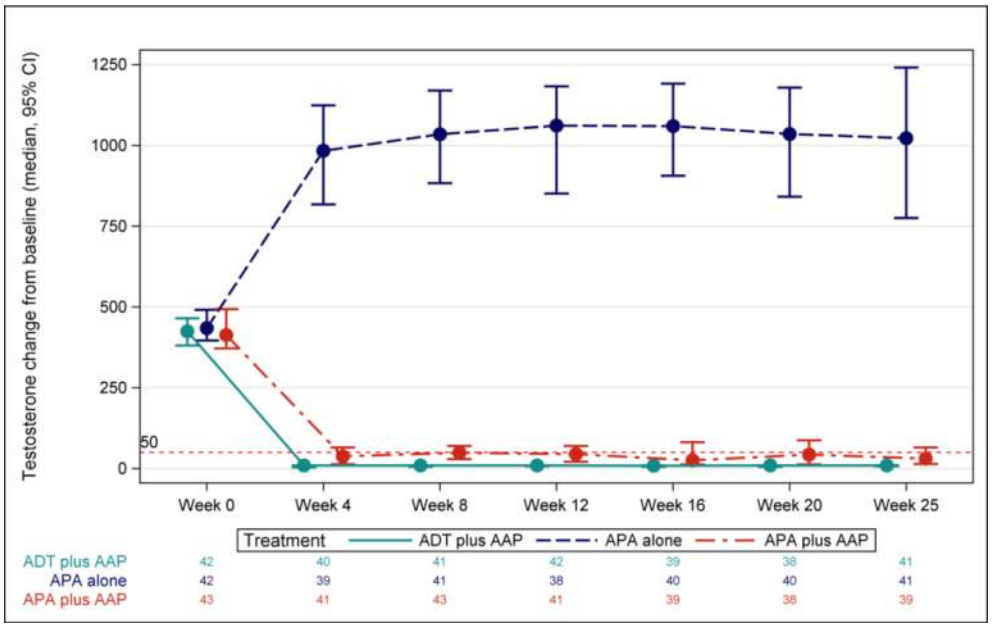

Fig. 2. **Median testosterone level change from baseline up to week 25.** Datapoints are medians, and whiskers depict 95% CI.

Table 3
All adverse events.

Adverse Event, *n*(%)	ADT plus AAP (N = 42)		APA (N = 42)		APA plus AAP (N = 44)	
	All grade	**Grade 3–4**	**All grade**	**Grade 3–4**	**All grade**	**Grade 3–4**
Gynaecomastia	3 (7)	0	23 (55)	0	9 (20)	0
Hot flushes	16 (38)	0	2 (5)	0	13 (30)	0
Fatigue	7 (17)	0	9 (21)	1 (2)	13 (30)	0
Hypertension	9 (21)	5 (12)	2 (5)	1 (2)	9 (20)	5 (11)
Rash	0	0	11 (26)	5 (12)	8 (18)	3 (7)
Back pain	8 (19)	0	5 (12)	0	4 (9)	1 (2)
Nausea	4 (10)	0	3 (7)	0	8 (18)	0
Pruritus	1 (2)	0	7 (17)	1 (2)	6 (14)	2 (5)
Diarrhoea	5 (12)	0	2 (5)	0	6 (14)	2 (5)
Oedema limbs	7 (17)	0	2 (5)	0	2 (5)	0
Headache	4 (10)	0	2 (5)	0	4 (9)	0
Hyperglycemia	4 (10)	2 (5)	1 (2)	0	5 (11)	2 (5)
Leg pain	5 (12)	0	3 (7)	0	1 (2)	0
Upper respiratory infection	4 (10)	0	1 (2)	0	4 (9)	0
Breast pain	0	0	6 (14)	0	2 (5)	0
Urinary infection	4 (10)	1 (2)	2 (5)	1 (2)	2 (5)	1 (2)
Vertigo	4 (10)	1 (2)	2 (5)	0	2 (5)	0
Myalgia	2 (5)	0	5 (12)	0	1 (2)	0
Anaemia	4 (10)	1 (2)	1 (2)	0	1 (2)	0

Data are n (%). All events occurring in ≥10% of patients in any arm.

4. Discussion

To our knowledge, this is the first randomized study to evaluate the efficacy and safety of ASI, alone or in combination, both without ADT, in patients with advanced CSPC. As a proof-of-concept study, patients with metastatic (74.2%), high-risk biochemical recurrence (17.2%), and locally advanced (8.6%) CSPC with an indication for ADT were included to evaluate the activity of ADT-free treatment alternatives in terms of PSA response. The proportion of patients with PSA of ≤0.2 ng/mL at week 25 was similar in arms ADT plus AAP (75.6%) and APA plus AAP (79.5%), while the APA arm showed a slightly lower rate (60.0%). PSA of ≤0.2 ng/mL at week 25 was validated as a potential surrogate endpoint for OS in previous only ADT studies [17]. Moreover, other randomized trials also evaluated the same endpoint in advanced CSPC and a remarkably similar rate of patients with PSA of ≤0.2 ng/mL at week 25, 68.1% with ADT in combination with enzalutamide (ARCHES trial) and 68.4% with apalutamide (TITAN trial) [10,11] was observed. Therefore, the observation of

similar proportions of patients with PSA of ≤0.2 ng/mL at week 25 in those treated with ADT plus AAP, APA, and APA plus AAP seems reassuring of the potential long-term efficacy outcome. However, it should be noted that our study also included non-metastatic patients, which could have overestimated our efficacy results compared to ARCHES and TITAN [10,11].

Additionally, most patients treated with APA plus AAP (97.4%) and APA (90.0%) had a PSA decline of ≥80%, similar to the 100% treated with ADT plus AAP. PSA decline of ≥80% as primary endpoint was reported by others [13,20]. Although the APA arm did not reach the predefined primary endpoint, an encouraging PSA decline of ≥80% was observed, as reported in a single-arm study with enzalutamide in the same setting (92.5%), which included a lower proportion of metastatic patients (39.0%) compared to the present APA arm (76.2%) [13].

The AE profile was similar in ADT plus AAP and APA plus AAP, with all-grade hot flushes in 38% and 30%, respectively, versus 5% in the APA arm. These findings may correlate with the different testosterone kinetics observed in ADT plus AAP and APA plus AAP arms as compared to the APA arm. Hypertension was mainly observed in AAP treated patients with 21% and 20%, respectively for ADT plus AAP and APA plus AAP, vs. 5% in APA arm. All-grade fatigue was 30% in APA plus AAP, compared to 17% in ADT plus AAP and 21% in the APA arms. Additionally, more patients treated in APA plus AAP arm required treatment interruptions. Conversely, gynaecomastia (55%) and breast pain (14%) were more common in APA compared to APA plus AAP and ADT plus AAP arms. In this regard, a meta-analysis has shown that prophylactic radiotherapy, as well as daily tamoxifen, can significantly reduce the incidence of gynaecomastia and/or breast pain and therefore, one of these strategies should be considered in future studies. Also, the authors concluded that tamoxifen appears to be an effective alternative to radiotherapy as a therapeutic treatment in the presence of gynaecomastia, but its side effects and off-label use must be considered [21].

Interestingly, our study demonstrated for the first time that APA plus AAP might also promote a clinically significant decrease in testosterone levels, reaching castration levels in most patients. It has also been observed that abiraterone alone, a selective, irreversible inhibitor of CYP17, an enzyme that is critical in the production of androgens in the testes, adrenal glands, and prostate-tumour tissue, was associated with a significant, sustained decrease in testosterone levels due to suppression of the testosterone/androstenedione axis in humans [22,23]. Moreover, ongoing trials are evaluating neoadjuvant abiraterone in combination with apalutamide or enzalutamide in high-risk localized prostate cancer, and at the same time trials with an intensification of neoadjuvant ADT plus ASI have been reported [14,24–27]. Conversely, APA arm led to a clinically significant increase in testosterone levels, similar to what has been reported with enzalutamide alone in the same setting [13]. Interestingly, a prospective phase 2 study, including 60 patients with bone mCRPC who received enzalutamide 160 mg orally daily and had bone marrow biopsies before treatment and at 8 weeks of treatment have shown bone marrow and circulating testosterone levels increased, providing the first evidence in humans that enzalutamide suppresses AR signalling while inducing an adaptive feedback [28]. Nevertheless, the difference in testosterone levels with APA alone as compared to ADT plus AAP and APA plus AAP was not reflected in the overall HRQoL, which showed no difference among the three treatment arms. This observation needs further validation on long-term follow up with mature data.

This trial has several limitations that should be addressed: first, the randomized phase 2 non-comparative design with a limited number of patients, without statistical comparisons among three arms, and evaluation of short-term outcomes. Second, different patient populations (i.e. locally advanced disease, high-risk biochemical relapse and metastatic disease) were included. Third, PSA of ≤0.2 ng/mL at week 25 has been validated as a surrogate endpoint for OS, but not in CSPC treatments without ADT. Fourth, the lack of long-term data on exposure to the use of prednisone 10 mg QD since at the time our trial was designed, neither the LATITUDE nor the STAMPEDE trials results were available. Fifth, we did not use a central laboratory for testosterone evaluation. Finally, HRQoL assessment might have been impaired by a brief evaluation and the inclusion of mildly symptomatic advanced CSPC. Thus, our results should be interpreted as generating hypothesis.

5. Conclusion

In conclusion, this is the first randomized trial evaluating the efficacy and safety of ADT-free treatment for patients with advanced CSPC. ADT plus AAP and APA plus AAP arms achieved the primary endpoint with the predefined efficacy threshold of more than 65% of patients with PSA of ≤0.2 ng/mL at week 25, whereas the APA arm did not; therefore, it should not be pursued in the future studies in unselected advanced CSPC. Further evaluation in a phase 3 trial aimed to compare ASI with or without ADT is warranted.

Contributions of the authors

Concept and design: FM, GW, TS, AF.

Search and collection of the data: all authors.

Analysis of data and interpretation: FM, GW, FS, AS, DB, AF, RG.

Statistical analysis: RG.

First draft of the manuscript: FM, FS, AS, DB and AF.

All authors contributed to the content of the report and reviewed further drafts. All authors reviewed and approved the final report before submission. The authors take full responsibility for the scope, direction, and content of the report.

Role of the funder/sponsor

This study was funded by Janssen-Cilag, who supplied study drugs, reviewed the draft analysis plan, performed data monitoring, and provided critical review of the draft report, including interpretation, but had no role in data collection or data analysis. LACOG was the legal sponsor of the study and was responsible for the study design, data collection, data analysis, interpretation, and writing the study report. The corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit for publication.

Additional contributions

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Conflict of interest statement

FCM reports honoraria from Astellas Pharma, Bayer Shering Pharma, Bristol-Myers Squibb Brazil, Janssen Oncology, Med Sharp & Dohme; consulting or advisory role: Astellas Pharma, Bayer Shering Pharma, Bristol-Myers Brazil, Janssen Oncology, Merck Sharp & Dohme, & Dohme; research funding: Janssen- Cilag; and travel expenses: Bayer Shering Pharma and Merck Sharp & Dohme. FAS fees speaker: Janssen, Bayer, Astellas, MSD, BMS, and Roche; advisory board: Bayer, Astellas, Janssen, Pfizer, MSD, and BMS; and sponsored research (as principal investigator): Roche, BMS, MSD, Janssen, AstraZeneca. MAL fees speaker: Astellas, Janssen, Sanofi, Bayer; research grant: AMGEN, Ferring, AstraZeneca, ProScan; advisory board: ProScan, Janssen, Astellas; sponsored research: Ferring, Janssen, Bayer, GSK, Active Biotech; travel expenses: Janssen, AstraZeneca, Pfizer, Bayer. DBQM reports grants from Pfizer; personal fees and non-financial support from Janssen, outside the submitted work. DAB reports personal fees and non-financial support from Bayer, grants, personal fees and non-financial support from Janssen; grants, personal fees and non-financial support from Astellas; personal fees and non-financial support from Roche; personal fees and non-financial support from Merck Sharp Dome; personal fees and non-financial support from Bristol Myers Squibb, outside the submitted work. OS reports non-financial support from Janssen, during the conduct of the study. AS reports personal fees from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Lilly, Merck Serono, MSD, Novartis, Pfizer, Pierre Fabre, Roche; non-financial support from Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, Merck Serono, MSD, Pfizer, Roche, Sanofi; grants from Bristol-Myers Squibb, outside the submitted work. FMC reports grants from Janssen-Cilag; travel expenses from Janssen-Cilag and Zodiac. TMS reports grants from Janssen during the conduct of the study; other from Janssen employee, other from AMGEN outside the submitted work. VCF reports other from Janssen Pharmaceuticals during the conduct of the study; other from Janssen Pharmaceuticals outside the submitted work. RG reports other from Janssen Pharmaceuticals during the conduct of the study; other from Janssen Pharmaceuticals outside the submitted work. GW reports grants from Janssen-Cilag during the conduct of the study. RGJ reports grants from Janssen-Cilag during the conduct of the study. VCS reports grants from Janssen-Cilag during the conduct of the study; personal fees from Bayer, Janssen-Cilag and Bristol-Myers Squibb; non-financial support from Bayer and Janssen-Cilag outside the submitted work. APF reports personal fees BMS, Roche, Novartis, Janssen, Astellas, Merck, AstraZeneca; non-financial support from BMS, Roche, Janssen, Astellas, Merck, Ipsen, AstraZeneca outside the submitted work.

EHC, SPSM, FMC, FAP, AGJ, FAF and DH have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.032.

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