European Journal of Cancer 155 (2021) 127–135

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Maintenance versus discontinuation of androgen deprivation therapy during continuous or intermittent docetaxel administration in castration-resistant prostate cancer patients: A multicentre, randomised Phase III study by the Piemonte Oncology Network

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https://doi.org/10.1016/j.ejca.2021.06.034

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Received 16 January 2021; received in revised form 15 June 2021; accepted 19 June 2021
Available online 6 August 2021

KEYWORDS
Prostate cancer;
Castration-resistant;
Androgen deprivation therapy;
Intermittent docetaxel

Abstract ***Background:*** This study was designed to demonstrate the non-inferiority (NI) in overall survival (OS) of suspension of androgen deprivation therapy (ADT) versus maintenance and intermittent versus continuous docetaxel administration in metastatic castration-resistant prostate cancer (mCRPC) patients.
Patients and methods: mCRPC patients were randomised to first-line docetaxel with maintenance or suspension of ADT. Patients attaining a prostate-specific antigen (PSA) response after four chemotherapy cycles underwent second randomisation to receive continuous or intermittent docetaxel therapy. Six hundred patients were to be randomised to achieve 80% statistical power to demonstrate an NI hazard ratio (HR) of 1.25 of interruption versus maintenance of ADT.
Results: The trial was prematurely closed when 198 participants were randomised. OS was similar in patients who continued (N = 96) versus those who interrupted (n = 102) ADT during docetaxel therapy (HR 0.98, 95% confidence interval [CI] 0.72–1.33] and those on a continuous (N = 35) versus an intermittent (N = 42) docetaxel schedule (HR 0.86, 95% CI 0.55–1.43). No difference in radiological progression-free survival, PSA response, or toxicity was observed between the study arms. The actual NI hazard margins of OS in Arms A and B patients were 1.33 and 1.43, respectively.
Conclusions: This trial enrolled one-third of the planned patients; this main weakness dramatically limits the interpretation of the results. ADT discontinuation and switching to an intermittent schedule did not seem to affect docetaxel efficacy. The absence of testosterone recovery in the majority of patients could have been a contributory factor. In men with mCRPC, ADT discontinuation should only be done with regular biochemical and clinical monitoring, with the option of quickly restarting ADT at disease progression.

1. Introduction

Docetaxel improves survival in men with metastatic castration-resistant prostate cancer (mCRPC) and is a standard therapy in this setting. Previous androgen deprivation therapy (ADT) was maintained during docetaxel in two pivotal trials [1,2], as recommended by current international guidelines [3]. One [4] of five retrospective studies [4–8] on the efficacy of ADT maintenance during chemotherapy in castration-resistant prostate cancer patients showed a survival advantage of the combination treatment. Up to ten docetaxel cycles are recommended in the management of mCRPC patients; however, long-term administration is associated with adverse effects and a negative impact on quality of life (QoL) [9].

An intermittent schedule has the advantage that prolonged exposure is minimised and long-term are toxicities prevented [10,11]. Here, we report the findings of a multicenter, prospective randomised clinical trial conducted by the Piemonte Oncology Network to test in mCRPC patients the non-inferiority (NI) of interruption versus maintenance of ADT during docetaxel administration and the intermittent versus the continuous docetaxel schedule.

2. Patients and methods

2.1. Study design and participants

This randomised Phase 3 study involved 19 Italian oncology centres (see Appendix 1) (NCT01224405, Eudract 2010-019004-24). The main inclusion criteria were histologically confirmed prostate adenocarcinoma, a metastatic disease that had progressed to ADT despite castrate serum testosterone levels (≤50 ng/dL); Eastern Cooperative Oncology Group performance status ≤2; and adequate hepatic, renal, and bone marrow function. The main exclusion criteria were elevated prostate-specific antigen (PSA) without radiological progression, prior cytotoxic chemotherapy, history of other

cancers, brain metastases, peripheral neuropathy, and other serious medical conditions.

The trial was approved by the ethics committee of each study site. A written, informed consent was obtained from all patients.

2.2. Randomization and treatment

Patients were randomly assigned in permuted blocks (sizes 4, 8, and 12) to receive docetaxel for four cycles with maintenance (Arm A) or suspension (Arm B) of ADT. The randomization sequence was stratified by each study centre where the patients were enrolled. The patients initially received four cycles of intravenous docetaxel (75 mg/m^2 on Day 1 every 21 days) together with oral prednisone (5 mg BID).

ADT was stopped till disease progression in Arm B patients and then resumed. Patients with radiological progression after Cycle 4 were withdrawn from the study and followed up till death. In patients without radiological progression and increased, stable, or a <50% decrease in PSA from baseline, docetaxel was continued till radiological or clinical progression, unacceptable toxicity, or for a maximum of ten cycles.

Patients attaining a PSA response after four cycles (>50% reduction from baseline) underwent second randomisation to continue docetaxel till progression or completion of ten cycles (Arm AB1) or interrupt docetaxel until PSA rose by 50% (at least 10 ng/mL) or disease progression (Arm AB2), at which time treatment was resumed (Fig. 1).

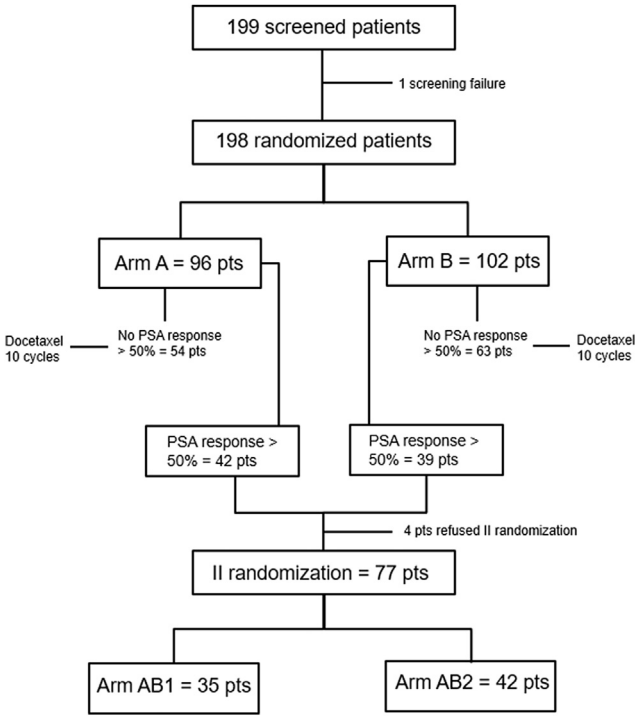

Fig. 1. Consort diagram.

Physical examination and baseline blood tests were repeated at 3-week intervals during docetaxel therapy. Serum PSA and serum testosterone levels were measured at baseline, after four docetaxel cycles, and every 3 months thereafter till disease progression. Imaging studies (computed tomography and bone scans) were performed at baseline, every 6 months, as well as to document radiological progression if PSA increased by >25%, bone pain worsened, or physical condition deteriorated. Bone pain and QoL were assessed via the McGill pain questionnaire and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, respectively [12,13], at baseline, at the end of Cycle 4, and every 6 months thereafter.

2.3. Outcomes

The primary efficacy outcome was overall survival (OS), defined as the interval from randomisation to death from any cause or to the date at which the patient was last known to be alive. The secondary outcomes were time to biochemical progression after first and second randomisation, measured as the interval from randomisation to the earliest event of PSA progression, clinical progression, death from any cause, or the last known date of follow-up without PSA progression; time to metastatic progression from the first and second randomisation, defined as time to the earliest sign of radiographic progression; PSA response, defined as a reduction of >50% over baseline in two or more PSA measurements obtained at least 4 weeks apart; frequency of severe toxicity at each course of chemotherapy and every 3 months during follow-up according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) [14]; QoL assessment (FACT-P questionnaire at baseline, at the end of Cycle 4 of chemotherapy, and every 6 months thereafter).

2.4. Statistical analysis

The main objective of the study was to demonstrate the NI in the survival of ADT suspension versus maintenance (Arm A versus Arm B) and to demonstrate the NI in the survival of intermittent versus continuous docetaxel (Arm AB1 versus AB2). The sample size was calculated in relation to the comparison between Arm A and Arm B and based on an alpha error (one sided) of 0.05, beta error of 0.20, hazard ratio (HR)of 1.25, below which the experimental group can be considered not inferior to the standard group, expected OS of 30% at 2 years, 4-year enrolment period, minimum follow-up of 2 years, and interim analysis (according to O'Brien and Fleming) planned at the end of year 3.

Based on these assumptions, 566 patients had to be enrolled, and at least 460 events (using a log-rank test) recorded to demonstrate NI between arms A and B with the predefined delta. Furthermore, assuming that 5% of

patients would be unavailable for the main analysis because of loss to follow-up or violation of study eligibility criteria, the planned enrolment was a total of 600 patients.

At the end of the first four docetaxel cycles, approximately 55% of patients were expected not to have attained a reduction of at least 50% in basal PSA or to have experienced disease progression; accordingly, 270 patients would have undergone second randomisation. This estimated sample size for the second comparison would have yielded a statistical power of at least 73%, with a minimum follow-up of 36 months from the second randomisation, an NI limit (HR 1.33, one-tailed alpha error 0.05). A comparison between Arm AB1 and Arm AB2 was planned when approximately 250 total deaths had occurred in the group eligible for second randomisation.

All randomised patients were included in the analysis according to the intention-to-treat principle, as were treated subjects per protocol. OS and disease-free survival were evaluated with the Kaplan–Meier method and compared with the log-rank test. The Cox model was used to estimate the HRs and confidence intervals (95%) adjusted for the main prognostic factors. The proportion of toxicity and responses in the two arms was compared using the chi-squared or Fisher's exact test, as appropriate.

In an ancillary study, we explored the prognostic role of serum testosterone levels in Arm B patients. To reduce the inherent bias of patients with early progression and death, and as no increase in testosterone was expected in the first weeks after stopping ADT, survival analyses were performed at Month 3 as a fixed landmark point. Patients who experienced disease progression or death before the landmark point were excluded from the analysis.

3. Results

3.1. Patient characteristics

Of a total of 199 eligible patients, 198 were randomly allocated to receive either docetaxel 75 mg/m^2 every 3 weeks with the maintenance of ADT (Arm A, n = 96)

Table 1
Patient characteristics.

Patients characteristics	Arm A (ADT suspension, N = 96), n (%)	Arm B (ADT maintenance, N = 102), n (%)	P
Median age (range)	64.86 (47–78)	65.19 (50–79)	0.87
Stage at diagnosis			
Stage I	1 (1)	0	0.67
Stage II	19 (19.8)	18 (17.6)	
Stage III	24 (25)	30 (29.4)	
Stage IV	52 (54.2)	54 (52.9)	
Gleason score			
<7	9 (9.4)	11 (10.8)	0.24
7	34 (35.4)	25 (24.5)	
>7	53 (52.2)	66 (64.7)	
PSA at diagnosis, median (range)	19 (0–2531)	21.8 (0–1072)	0.66
PSA at randomisation, median (range)	57.35 (1.23–2995)	48.9 (4.9–1146)	0.91
Treatment at diagnosis			
Radical prostatectomy	44 (45.8)	39 (38.2)	0.32
Radiation therapy	19 (19.9)	19 (18.6)	
Androgen deprivation therapy	32 (33.3)	39 (38.2)	
Observation	1 (1)	5 (4.9)	
Time from metastatic disease to first randomisation (months), median (range)	10.32 (0–122)	10.27 (0–193)	0.94
Disease-free survival (months), median (range)	35.82 (5–184.23)	33.88 (4.23–208.6)	0.99
Disease sites at inclusion in the trial			
Prostate	9 (9.4)	17 (16.7)	0.11
Bone	65 (67.7)	91 (89.2)	
Lymph nodes	49 (51)	38 (37.3)	
Soft tissue	2 (2.1)	5 (4.9)	
Visceral	17 (17.7)	15 (14.7)	
No of metastatic sites			
1	58 (60.4)	55 (53.9)	0.27
2	28 (29.2)	32 (31.4)	
>2	10 (10.4)	15 (14.7)	
ECOG PS at randomization			
0	66 (68.8)	78 (76.5)	0.22
1	30 (31.3)	24 (23.5)	
>1	0	0	
Median BMI (range)	27.04 (17–38)	27.47 (3–53)	0.97
Median testosterone levels at randomisation (range)	0.11 (0-0.5)	0.10 (0-0.5)	0.90

BMI, body mass index.

or docetaxel 75 mg/m^2 every 3 weeks with ADT suspension (Arm B, n = 102; Fig. 1). Baseline patient and tumour characteristics were similar for both groups (Table 1). One-half of the patients in both groups had Stage IV disease at diagnosis. Bone was the most frequent site of metastases: 65 (68%) Arm A and 91 (89%) Arm B patients, respectively.

3.2. Efficacy

The median duration of follow-up was 88.5 months: PSA has increased preceding radiological progression in 185 (93%) patients, radiological progression occurred in 188 (95%), and 165 (83%) died. The median OS was 23.3 months in Arm A and 24.8 months in Arm B patients (HR 0.98, 95% CI 0.72–1.33; Fig. 2a). The actual NI margin of OS was an HR of 1.33. The median biochemical progression-free survival (bPFS) was 8.0 months and 6.2 months (HR 1.13, 95% CI 0.85–1.51; Fig. 2b), and the median clinical/radiological progression-free survival (c/rPFS) was 10.3 months and 10.8 months (HR 0.98, 95% CI 0.73–1.31; Fig. 2c) in Arm A and Arm B patients, respectively. After four cycles of docetaxel, PSA was reduced >50% in 42 (43.8%) Arm A and 39 (38.2%) Arm B patients; PSA was reduced <50% in 31 (32.2%) and 35 (34.3%) and increased in 23 (24%) and 28 (27.5%) Arm A and Arm B patients, respectively.

3.3. Toxicity

The most frequent adverse events were gastrointestinal (nausea, vomiting, and diarrhoea), fatigue, and neutropenia. Adverse event frequency and severity were similar in the two groups (Table 2).

3.4. Serum testosterone levels and disease outcome

Testosterone serum levels after four docetaxel cycles were above the castration threshold (0.5 mg/dl) in 19 (18%) Arm B patients and within the normal range in only two patients. We evaluated the prognostic effect of serum testosterone above the castration range. Four patients relapsed or died within the first 3 months (landmark point), so the analysis was performed in 98 assessable patients. The median OS was 24.8 months in the castrated (T–) and 27.5 months in the patients with testosterone levels above the castration range (T+; HR 0.75, 95% CI 0.46–1.3; Fig. 3). The median c/rPFS was 11.5 months in the T+ and 10.4 months in the T– patients (HR 1.04, 95% CI 0.61–1.77); the median bPFS was 8.2 and 6.2 months, respectively (HR 0.75, 95% CI 0.44–1.30), data not shown. Serum testosterone levels at subsequent time points were unavailable in most patients and were not analysed.

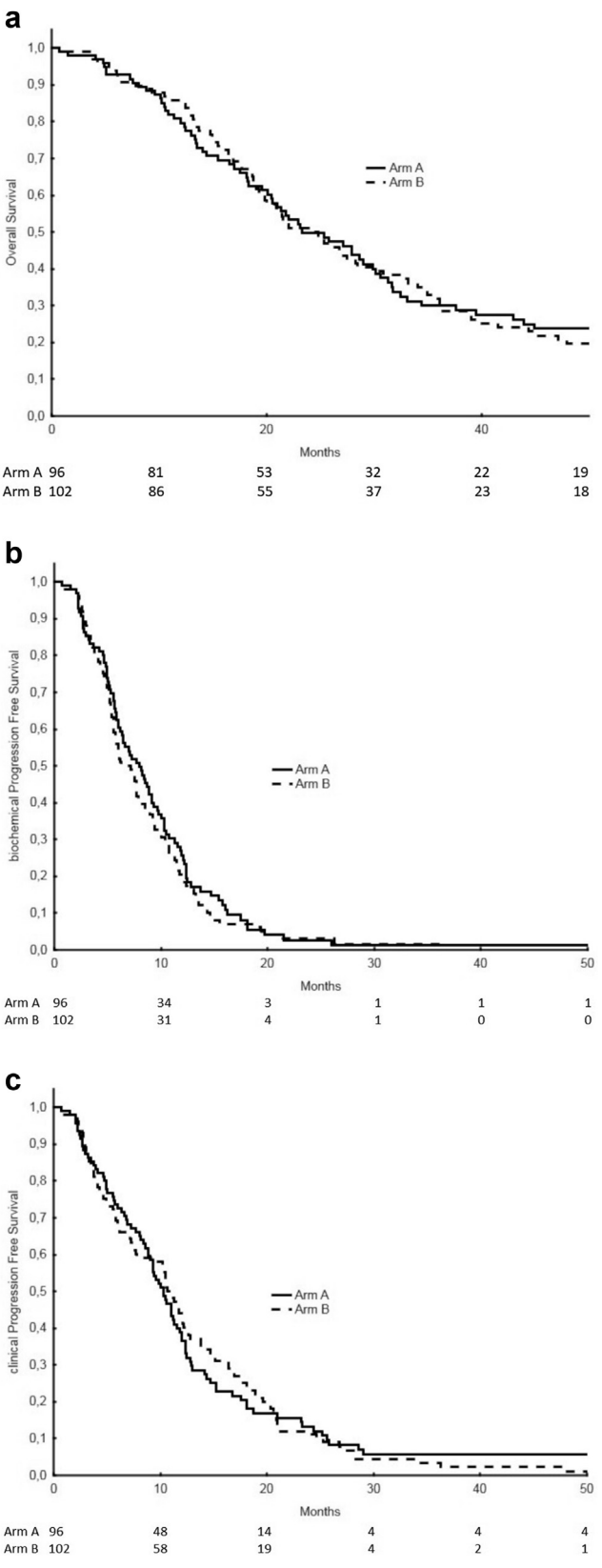

Fig. 2. **(A)** Kaplan–Meier curves of overall survival of Arm A and Arm B patients. **(B)** Kaplan–Meier curves of biochemical progression-free survival of Arm A and Arm B patients. **(C)** Kaplan–Meier curves of clinical progression-free survival of Arm A and Arm B patients.

Table 2
Toxicity.

Toxicity grade	Arm A (N = 96), n (%)	Arm B (N = 102), n (%)	P
Gastrointestinal			
0	58 (60.4)	61 (60.4)	0.93
1–2	30 (31.3)	40 (39.2)	
3–4	8 (8.3)	1 (1)	
Neurological			
0	67 (69.8)	77 (75.5)	0.37
1–2	29 (30.2)	24 (23.5)	
3–4	0 (0)	1 (1)	
Neutropenia			
0	71 (74)	69 (67.7)	0.56
1–2	9 (9.3)	10 (9.8)	
3–4	16 (16.7)	23 (22.5)	
Anaemia			
0	70 (72.9)	71 (69.6)	0.86
1–2	24 (25)	29 (28.4)	
3–4	2 (2.1)	2 (2)	
Thrombocytopenia			
0	88 (91.7)	94 (92.2)	0.81
1–2	6 (6.3)	7 (6.9)	
3–4	2 (2.1)	1 (1)	
Fatigue			
0	59 (61.5)	53 (52)	0.15
1-2	33 (34.4)	38 (37.3)	
3-4	4 (4.2)	11 (10.8)	
Alopecia			
0	78 (81.3)	80 (78.4)	0.65
1–2	12 (12.5)	12 (11.8)	
3–4	6 (6.3)	10 (9.8)	
Nail changes			
0	81 (84.4)	88 (86.3)	0.57
1–2	14 (14.6)	14 (13.7)	
3–4	1 (1)	0 (0)	

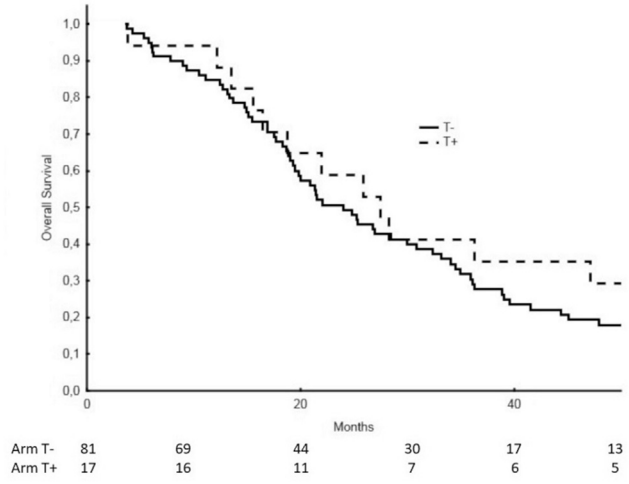

Fig. 3. Kaplan–Meier curves of overall survival in patients attaining testosterone levels above the castration levels (T+) compared with those who did not (T–). A landmark at 3 months was introduced.

3.5. Intermittent versus continuous docetaxel administration

Four of the 81 patients eligible for the second randomisation refused to participate in this second study and continued with docetaxel till progression or ten cycles. Among the remaining 77 patients, 35 were randomised to continuous (Arm AB1) and 42 to intermittent docetaxel (Arm AB2). OS was 28.7 and 31.8 months in the Arm AB1 and the Arm AB2 patients, respectively (HR 0.86, 95% CI 0.55–1.43; Fig. 4), whereas c/rPFS was 8.27 and 9.2 months in the two arms, respectively (HR 1.13, 95% CI 0.72–1.79). The median bPFS was longer in the AB2 patients (intermittent schedule) than in the AB1 patients (continuous schedule): 6.1 versus 2.7 months (HR 2.6, 95% CI 1.6–4.2; Figs. S1–S2, Supplementary Material).

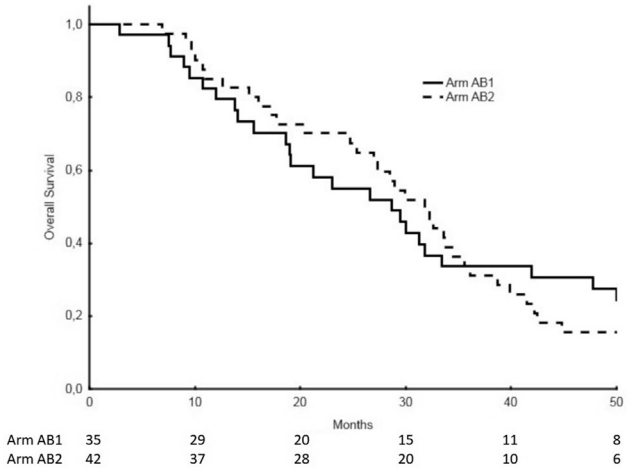

Fig. 4. Kaplan–Meier curves of overall survival of patients submitted to continuous (Arm AB1) or intermittent (Arm AB2) docetaxel schedule administration after PSA response at four cycles.

3.6. Quality of life

Patients completed the FACT-P questionnaire at baseline, at the end of four cycles of chemotherapy, and at 6 months after randomisation: 101 at baseline and Cycle 4 (first randomisation) and 67 at 6 months. Only 30 of the 77 (39%) completed the questionnaire at second randomisation. No statistically significant changes in QoL for the two groups were noted (Fig. 5).

4. Discussion

Our findings suggest a similar survival perspective for the patients who interrupted ADT during docetaxel therapy and those who maintained it. We observed no significant difference in the secondary end-points between the two treatment arms: radiological progression-free survival, bPFS, and PSA response. Although these data are original and of potential interest, our study has several limitations. First, the accrual was less than that needed to achieve sufficient power to adequately address the NI in OS between the two arms. Therefore, the

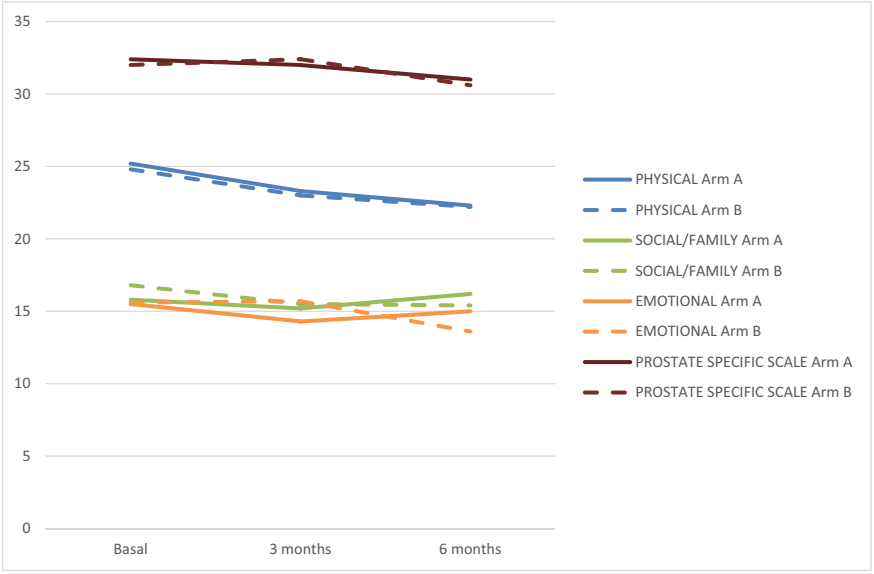

Fig. 5. Changes in quality of life at baseline and at 3 and 6 months after first randomization.

preplanned NI hazard margin of 1.25 increased to 1.33, considering the actual accrual of the study. Second, the comparison between the intermittent and the continuous docetaxel schedule was clearly underpowered: the NI hazard margin was 1.43.

Furthermore, our assumption was that suspension of ADT would have resulted in an increase in testosterone levels in a consistent number of patients and that this increase would not have been detrimental. Unfortunately, only 7% of patients randomised to the ADT withdrawal arm achieved a serum testosterone level >0.5 ng/ml after 3 months. This contrasts with intermittent androgen withdrawal studies that demonstrated that the time to increase in testosterone above the castration threshold is about 3 months in the off-therapy phase [15,16]. The long-term ADT exposure may have induced testicular atrophy in the majority of our patients, which prevented the restoration of testosterone synthesis after ADT suspension. A previous study reported that most patients who had received long-term ADT therapy (>4 years) remained castrated for up to 2.5 years after therapy cessation [17]. These data notwithstanding, the outcome was not worse in the patients attaining serum testosterone >0.5 ng/ml at 3 months; the median survival was 4 months longer than for their counterparts with levels within the castration range, although this difference was not statistically significant.

A previous study found a direct relationship between serum testosterone levels and OS in mCRPC patients receiving docetaxel [18]. The prognostic role of testosterone levels in mCRPC was documented in a trial-based meta-analysis that included patients treated with new generation hormone therapies [19]. A plausible explanation for this apparent testosterone paradox is that higher testosterone levels during docetaxel therapy may maintain prostate cancer cells in a prolonged hormone-sensitive state, thus enhancing the efficacy of subsequent hormone therapies [20].

In our study, two Arm B patients obtained a significant clinical benefit after ADT resumption at disease progression to docetaxel [21]. No difference in docetaxel toxicity was observed between the two study arms, and no differences in overall score or single QoL items were observed in the subgroup in which QoL was assessed. A previous study demonstrated that docetaxel clearance is consistently increased in castrated men with potentially better tolerability but a reduction in drug efficacy. The failure to recover castration status by most of the Arm B patients could account at least in part for the lack of difference in efficacy and toxicity of docetaxel therapy between the two arms [22].

With regard to the intermittent docetaxel arm, nine single-arm Phase II studies [10] and one randomised clinical trial [11], the PRINCE study, differed in design and docetaxel schedule from our study in which we applied the criterion of a reduction of at least 50% in PSA to enter the study.

Our results suggest no difference in OS, progression-free survival (PFS), PSA response, and toxicity between the treatment arms, as reported by the PRINCE trial. But, again, our trial was dramatically underpowered. As observed in the PRINCE study, biochemical PFS was significantly longer in the intermittent arm, but this observation is of limited clinical impact [23].

There were no differences in QoL between the patients who maintained and those who temporarily suspended ADT. The short follow-up for QoL and the small number of patients whose testosterone rose above the castration threshold may explain these results.

In conclusion, in this trial, discontinuation of ADT and switching to an intermittent schedule did not seem

to change docetaxel efficacy, mainly because no biochemical signs of testosterone recovery were seen in many patients. This trial enrolled one-third of the planned patients, and this weakness dramatically limits the interpretation of the results. Nonetheless, our findings suggest that if ADT is discontinued, testosterone/PSA levels should be regularly monitored and patients clinically reviewed, with the option of quickly restarting ADT at progression.

Funding

This study was supported by a grant from the Piemonte Oncology Network.

Authors' contributions:

A.B. contributed to term, conceptualisation, and methodology. A.R.B. and G.C. contributed to software. A.B., S.B., M.Z., and G.C. contributed to validation. A.B., S.B., M.Z., and G.C. contributed to formal analysis. S.B., A.M., A.D.V., V.P., C.O., C.B., E.F., P.V., F.V., Z.S., I.C., O.D.C., C.M., C.S., D.A., F.M., A.C., A.R.B., S.B., A.G., M.T., E.N., M.F., and A.S. contributed to investigation. S.B., A.M., A.D.V., V.P., C.O., C.B., E.F., P.V., F.V., Z.S., I.C., O.D.C., C.M., C.S., D.A., F.M., A.C., A.R.B., S.B., A.G., M.T., E.N., M.F., and A.S. contributed to resources. A.B., S.B., M.Z., and G.C contributed to data curation. A.B., S.B., A.M., and A.D.V. wrote the article. A.B., A.M., S.B., and A.D.V. reviewed and edited the article. S.B. and A.D.V. contributed to visualisation. A.B. contributed to supervision and project administration. A.B., M.T., O.B., and B.C. contributed to funding acquisition.

Conflict of interest statement

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 article.

Acknowledgements

The authors thank Davide Zanon for his assistance with the English language revision.

In memory of Dr. Cosimo Sacco, a truly great physician, researcher, colleague, and friend. In his professional life, he showed compassion and kindness to all, especially to his patients and their families. His premature death is a great loss to our group.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.06.034.

Appendix

The following collaborators were the investigators and co-authors of the study:

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