

Efficacy of Testosterone Suppression with Sustained-Release Triptorelin in Advanced Prostate Cancer

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ABSTRACT

Introduction: Androgen deprivation therapy (ADT) is a mainstay of treatment against advanced prostate cancer (PC). As a treatment goal, suppression of plasma testosterone levels to <50 ng/dl has been established over decades. Evidence is growing though that suppression to even lower levels may add further clinical benefit. Therefore, we undertook a pooled

retrospective analysis on the efficacy of 1-, 3-, and 6-month sustained-release (SR) formulations of the gonadotropin-releasing hormone (GnRH) agonist triptorelin to suppress serum testosterone concentrations beyond current standards.

Methods: Data of 920 male patients with PC enrolled in 9 prospective studies using testosterone serum concentrations as primary endpoint were pooled. Patients aged 42–96 years had to be eligible for ADT and to be either naïve to hormonal treatment or have undergone appropriate washout prior to enrolment. Patients were treated with triptorelin SR formulations for 2–12 months. Primary endpoints of this analysis were serum testosterone concentrations under treatment and success rates overall and per formulation, based on a testosterone target threshold of 20 ng/dl.

Results: After 1, 3, 6, 9, and 12 months of treatment, 79%, 92%, 93%, 90%, and 91% of patients reached testosterone levels <20 ng/dl, respectively. For the 1-, 3-, and 6-month formulations success rates ranged from 80–92%, from 83–93%, and from 65–97% with median (interquartile range) serum testosterone

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values of 2.9 (2.9–6.5), 5.0 (2.9–8.7), and 8.7 (5.8–14.1) ng/dl at study end, respectively.

Conclusion: In the large majority of patients, triptorelin SR formulations suppressed serum testosterone concentrations to even <20 ng/dl. Testosterone should be routinely monitored in PC patients on ADT although further studies on the clinical benefit of very low testosterone levels and the target concentrations are still warranted.

Keywords: Advanced prostate cancer; Castration limits; Hormonal therapy; Testosterone suppression; Triptorelin

INTRODUCTION

Based on recent estimates, prostate cancer (PC) ranks first among all new male cancers in both the USA and Europe (21% in 2016 and 22.8% in 2012, respectively) [1, 2]. Testosterone is known to foster PC cell growth; thus, the backbone therapy of advanced PC is androgen deprivation (ADT). Approximately 90% of tumours respond to initial ADT, which may result in a marked symptom reduction and prolonged survival, even if androgen-independent disease eventually develops [3–5].

ADT was initially achieved surgically via bilateral orchiectomy. Gonadotropin-releasing hormone (GnRH) analogues emerging in the 1980s offered a novel approach to medical castration through suppression of the hypothalamic-pituitary-gonadal axis. One of these was triptorelin, which was shown to be up to 100 times more potent than the native GnRH in vitro and in vivo [6–8]. Its clinical development started in 1982 [3] and it was registered as the first GnRH agonist SR formulation worldwide in France in 1986. Today, GnRH agonists are used worldwide for

ADT [9] with survival rates similar to surgical castration [10]. They reduce serum testosterone to castrate levels via the decrease in pituitary gonadotropin secretion that follows down-regulation of the pituitary GnRH receptors [11]. The ensuing hypoandrogenic environment results in glandular and tumour shrinkage and in an increase of interglandular connective tissue [4, 12, 13].

A testosterone level of 50 ng/dl (1.7 nmol/l) has been established as the standard castration threshold, which has been applied for over 40 years [14]. This threshold is widely accepted by regulatory authorities for the approval of GnRH analogues in the treatment of advanced PC [14, 15] and is also deemed adequate by the National Comprehensive Cancer Network (NCCN) [16]. The European Association of Urology (EAU) indeed also acknowledges the 50 ng/dl cut-off, but suggests 20 ng/dl (0.7 nmol/l) to be more appropriate as “better results are repeatedly observed with lower levels compared to 50 ng/dl” [17].

In fact, there is growing evidence that the extent of testosterone suppression during ADT in hormone-sensitive PC patients predicts a lower risk of and shorter time to androgen-independent progression or castration-resistant PC (CRPC), although so far most studies have been retrospective and sample sizes were rather small [4, 11, 14, 18–20]. Advances in the understanding of the principal mechanisms of PC progression and resistance to castration have led to new agents for CRPC such as the testosterone synthesis inhibitor *abiraterone* and the androgen receptor blocker *enzalutamide*. The improved survival in patients with metastatic CRPC when adding these agents to first-line ADT with GnRH analogues (or surgical castration) also indicates an important role of

low testosterone levels in the treatment of advanced PC [21, 22].

Efficacy results of triptorelin 1-, 3-, and 6-month formulations in patients with advanced PC have been published based on the standard castration limit of serum testosterone of 50 ng/dl. Reports suggesting that serum testosterone levels below this standard threshold might lead to improved clinical outcomes [4, 11, 14, 18–20] prompted us to re-examine testosterone data from nine phase II to IV studies, which is so far the largest analysis examining the efficacy of ADT at a cut-off level of 20 ng/dl [3, 9, 23].

METHODS

This is a retrospective pooled analysis of nine prospective clinical studies on the efficacy of triptorelin 1-, 3-, and 6-month SR formulations for advanced PC with overall 920 evaluable patients. Four studies were randomised controlled phase II studies, two were randomised controlled phase III studies, and three were non-controlled phase II to IV studies (Table 1). Primary endpoints always included testosterone assessments measured by either validated radioimmunoassay (RIA) or liquid chromatography tandem mass spectrometry (LC-MS/MS) [3, 9, 24, 25], which proved to show comparable results at both high and low testosterone concentrations. At the very low levels expected in men under ADT, RIA and LC-MS/MS are considered the most accurate and reliable methods.

Patients were recruited in Europe and South Africa and had to have an indication for ADT, i.e., advanced or metastatic PC or rising prostate-specific antigen (PSA) after failed local therapy, were naïve to hormonal

treatment or had undergone a 6-month washout period prior to study treatment, and presented with a normal baseline testosterone level at study entry. None of the patients except those in study E28-52014-701 (flutamide for 10 days) received any ADT. Concomitant treatments affecting the metabolism or secretion of testosterone were prohibited in all studies. Patients were treated with only one of the triptorelin formulations and investigated for 2–12 months (Fig. S1) except in study E28-52014-701 in which some patients were switched from the 1-month to the 3-month formulation (Table 1). All procedures performed in the original studies were in accordance with the ethical standards of institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients enrolled in the original studies; for the retrospective pooled analysis no formal consent is required.

Descriptive statistics were used to present demographic data, testosterone concentrations, and success rates. For the calculation of mean testosterone levels over various ranges of months, first the mean value for all available measurements over the indicated range of months was calculated for each patient without imputation for missing values, and then the mean and standard error (SE) for each group were calculated based on these means. For the comparison of baseline characteristics, Student's *t* test and chi-square test were used. Data pooling and data management were done in SAS[®] (version 9.4) and MS Access 2013. Analyses were performed and figures created with R Core Team (2016).

Table 1 Overview of the nine studies combined in this analysis (ITT populations = 920)

Study ID, location; number of patients	Study design	Treatment (triptorelin formulation); duration	Primary endpoints	Assay (sensitivity)
DEB-96-TRI-02 South Africa; <i>n</i> = 30	Phase II, open, 1-arm	Pamoate 3.75 mg (1-month) IM on days 0 and 28; 2 months	Response (inhibition of FSH and LH secretion) Triptorelin levels on days 0 and 28 Reduction of testosterone levels from day 0 to 56	¹²⁵ I-RIA Kit (LOD 6 ng/dl) ^b
DEB-99-TRI-04 South Africa; <i>n</i> = 69	Phase II, multicentre, single-blind, randomised, controlled, parallel group	Pamoate 3.75 mg (1-month) IM Acetate 3.75 mg (1-month) IM, both on days 1 and 29; 2 months	Testosterone pharmacodynamics	¹²⁵ I-RIA Kit (LOD 6 ng/dl) ^b
DEB-TRI6M-201 Bulgaria; <i>n</i> = 24 (8 ^a)	Phase II, single-blind, randomised, controlled, 3-arm	Pamoate 22.5 mg (6-month) IM; 6 months	Achievement of castrate testosterone levels on day 29 Maintenance of castrate levels from days 57 to 169	Solid-phase RIA (direct/extracted) (LOD 1 ng/dl)
E47-52014-402L UK; <i>n</i> = 70	Phase II, multicentre, open, randomised	Pamoate 11.25 mg (3-month) IM Acetate 3 mg (1-month) IM on days 0, 28, 56; 3 months	Testosterone level at month 3 (day 84)	Direct RIA (LOD 5 ng/dl)
E28-52014-701 South Africa, France, UK; <i>n</i> = 131	Part I: phase II, multicentre, open, randomised, 2-arm Part II: open extension, 1-arm	Acetate 11.25 mg (3-month) IM Acetate 3 mg (1-month) IM every 28 days; 3 months Acetate 11.25 mg (3-month) IM on days 91–273; 6 months	% Patients with testosterone levels ≤50 ng/dl at day 84	RIA (LLOQ 5 ng/dl)
DEB-96-TRI-01 1st South Africa; <i>n</i> = 335	Phase III, multicentre, randomised, controlled, 2-arm	Pamoate 3.75 mg (1-month) IM every 28 days Pamoate 11.25 mg (3-month) IM every 84 days; 9 months	Achievement of testosterone castration levels at month 1 Maintenance of castration levels from month 2 to 9	¹²⁵ I-RIA Kit (LOD 6 ng/dl) ^b

Table 1 continued

Study ID, location; number of patients	Study design	Treatment (triptorelin formulation); duration	Primary endpoints	Assay (sensitivity)
DEB-96-TRI-01 2nd South Africa; <i>n</i> = 277 (137 ^a)	Phase III, multicentre, randomised, controlled, 2-arm	Pamoate 3.75 mg (1-month) IM every 28 days; 9 months	Achievement of testosterone castration levels at day 29 Maintenance of castration levels from month 2 to 9	¹²⁵ I-RIA Kit (LOD 6 ng/dl) ^b
DEB-TRI6M-301 South Africa; <i>n</i> = 120	Phase III, multicentre, open-label, 1-arm	Pamoate 22.5 mg (6-month) IM on days 1 and 169; 12 months	Achievement of testosterone castration levels at day 29 Maintenance of castration levels from month 2 to 12	LCMS/MS (LLOQ 3 ng/dl)
DEB-01-TRI-04 South Africa; <i>n</i> = 20	Phase IV, open-label, 1-arm	Pamoate 11.25 mg (3-month) IM on days 1, 85, and 169; 9 months	% Castrated patients on days 87 and 171, two days after re-exposures to triptorelin pamoate	DiaSorin RIA (LOD 2.9 ng/dl)

FSH follicle-stimulating hormone, *GnRH* gonadotropin-releasing hormone, *IM* intramuscular, *LH*: luteinising hormone, *LLOQ* lower limit of quantification, *LOD* limit of detection

^a Only patients of the triptorelin arm were included in this analysis

^b From kit instruction manual

Table 2 Demographic data and baseline characteristics, means (range) or *n* (%)

Triptorelin formulation	1 month (3.75 mg)	3 month (11.25 mg)	6 month (22.5 mg)	All
Patients enrolled	489	303	128	920
Age (years)	71.1 (42–96)	70.5 (48–93)	71.1 (51–93)	70.9 (42–96)
Weight (kg)	74.2 (40–129)	74.6 (38–132)	83.3 (47–136)	75.8 (38–136)
BMI (kg/m ²)	24.8 (13–43)	25.2 (16–44)	27.6 (19–42)	25.4 (13–44)
Testosterone (ng/dl)	358.6 (3–1015)	383.1 (40–1296)	502.6 (54–1171)	386.7 (3–1296)
Race ^a , <i>n</i> (%)	421 (100)	240 (100)	128 (100)	789 (100)
Caucasian	231 (54.9)	147 (61.2)	85 (66.4)	463 (58.7)
Black	128 (30.4)	65 (27.1)	27 (21.1)	220 (27.9)
Coloured	61 (14.5)	27 (11.3)	16 (12.5)	104 (13.2)
Other	1 (0.2)	1 (0.4)	0 (0)	2 (0.2)

BMI body mass index

^a Data on ethnicity were not collected in study E28-52014-701

RESULTS

Mean age was similar among formulation groups with ages ranging from 42 to 96 years. Overall, half of the patients were Caucasian and one quarter black (Table 2). The 6-month formulation group had significantly higher testosterone levels as compared to the other two groups at baseline, i.e., means (95% CIs): 358.6 (345.8; 371.4) ng/dl in the 1-month formulation group and 383.1 (363.5; 402.7) ng/dl in the 3-month formulation as compared to 502.6 (467.4; 537.8) ng/dl in the 6-month formulation group (Table 2). The mean BMI was also higher in the 6-month formulation group as compared to the others.

The pooled data of all studies showed that a high proportion of patients achieved a testosterone level <20 ng/dl at the time points pre-defined in the protocols (i.e., months 1, 3, 6, 9, and 12), regardless of the formulation. Overall success rates based on the castration limit of 20 ng/dl reached 79% (95% CI: 75.9–81.3%) at month 1, 92% (89.7–93.6%) at

month 3, 93% (90.4–94.4%) at month 6; 90% (87.2–92.0%) at month 9, and 91% (84.6–95.8%) at month 12. The success rates based on the standard castration limit of 50 ng/dl ranged from 95–99% (Fig. 1).

Overall, mean testosterone levels were maintained <20 ng/dl over study periods for all formulations except for the 6-month formulation at months 1 and 12 (Fig. 2) because of single patients with exceptionally high levels (patient DEB-TRI6M-301-11-11613 with a value 422 ng/dl at month 1 and patient DEB-TRI6M-301-04-04602 with a value of 1213 ng/dl at month 12). Excluding those as outliers would result in mean values of 18.5 and 13.1 ng/dl, respectively.

Success rates per formulation in terms of the proportion of patients with testosterone <20 ng/dl ranged from 80–92% for the 1-month formulation, 83–93% for the 3-month formulation, and 65–97% for the 6-month formulation (Fig. 1b). The large majority of patients (89.7%) maintained stable low testosterone levels without two

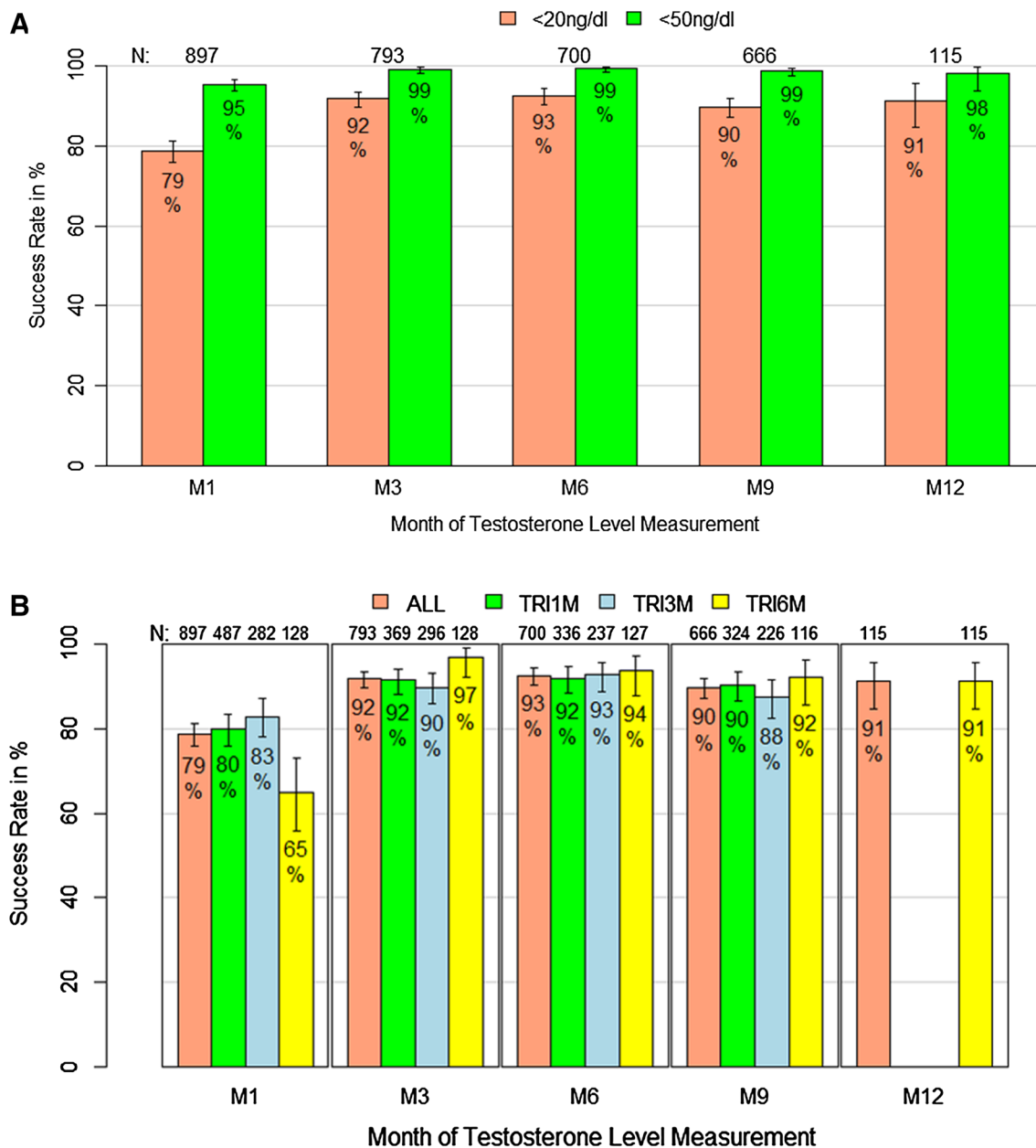


Fig. 1 a Proportion of patients achieving a testosterone level <20 or <50 ng/dl at months 1, 3, 6, 9, and 12 after treatment with any triptorelin formulation. **b** Proportion of patients achieving a testosterone level <20 ng/dl overall

and per each formulation (TRI1M: 1-month; TRI3M: 3-month; TRI6M: 6-month, the only formulation with 12-month data available). *Tick marks* indicate the exact 95% CI. *N* number of patients with testosterone data

consecutive increases in serum testosterone to ≥ 20 ng/dl. Only very few patients (1.1%) experienced such testosterone escapes to ≥ 50 ng/dl. Pooling data from all

formulations resulted in mean testosterone levels just above 10 ng/dl for months 1–6, 1–9, and 1–12. Testosterone still decreased between months 1 and 2 and mean values were <10 ng/

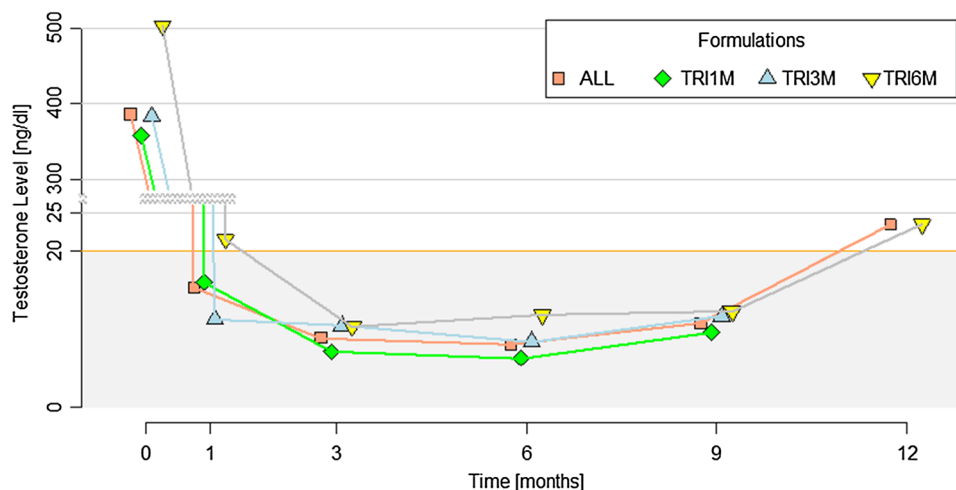


Fig. 2 Mean serum testosterone levels (ng/dl) versus selected time points (months) for each and all formulations—partly zoomed scale. The time values for the different formulations (all, TRI1M: 1-month, TRI3M:

dl for months 2–6, 2–9, and 2–12 (Fig. S2). At the end of the studies, median (IQR) serum testosterone values were 2.9 (2.9–6.5) ng/dl for the 1-month formulation, 5.0 (2.9–8.7) ng/dl for the 3-month formulation, and 8.7 (5.8–14.1) ng/dl for the 6-month formulation.

DISCUSSION

Our analysis of pooled testosterone data was based on a total of almost 1000 patients and is, so far, the largest of its kind. The great majority of patients treated with triptorelin were shown to achieve and maintain testosterone levels <20 ng/dl. This is in line with two other retrospective studies reassessing testosterone levels achieved by either orchiectomy [14] or by use of polymer-delivered subcutaneous leuprolide acetate formulations [26]. Suppression of testosterone levels <20 ng/dl through ADT may thus be common and regardless of the formulation, although in our study, the testosterone decrease with the 6-month formulation appeared less rapid. However, this might have been due to a

3-month, and TRI6M: 6-month formulation) are slightly offset to distinguish the corresponding measurements for each formulation

slightly different patient population as reflected by higher baseline BMI and testosterone levels. In fact, obese patients were reported to respond less to GnRH agonist treatment as compared to patients with normal BMI [27]. By contrast, the efficacy of the triptorelin 6-month formulation has recently been confirmed by a Danish study with patients under triptorelin showing significantly lower testosterone levels at months 3 and 6 than after subcapsular orchiectomy [28].

Still, some limitations of our study may need to be considered: Safety data of the nine studies were not pooled and re-analysed as the overall safety profile of triptorelin treatment in PC has recently been confirmed to be well-established and consistent among formulations as well [29]. A more relevant limitation might be inherent to the retrospective design. Although all included clinical trials were quite homogeneous in terms of design, quality, enrolled populations, and analytical methods for the measurement of testosterone, they were of rather short

duration and did therefore not allow for an assessment of the time to androgen-independent progression (AIP) or death. Thus, the clinical benefit of achieving testosterone levels <20 ng/dl could actually not be addressed. However, evidence is growing that such a benefit indeed exists, even though most studies so far have been retrospective as well and rather small in size.

In 73 PC patients on ADT followed up for 51 months (range 1–20 years) the lowest serum testosterone cut-off that was able to discriminate regarding AIP-free survival was 32 ng/dl (88 vs. 137 months; $P < 0.03$). However, only breakthrough testosterone increases >50, but not >20 ng/dl had a significant impact on AIP-free survival [18]. In 225 Japanese PC patients treated with combined androgen blockade and followed up for 45.8 months, multivariate analysis revealed nadir testosterone <20 ng/dl to be the most significant prognostic factor of overall survival [20]. The risk of death was also shown to significantly correlate with 6-month serum testosterone levels in 129 patients with metastatic PC treated with goserelin and followed up for 47.5 months (range 22–72) [11]. In the largest and longest retrospective study so far with 626 PC patients having received ADT for a median of 8 years, nadir testosterone levels <20 ng/dl were shown to be associated with longer times to disease progression [30]. Conversely, patients with a median testosterone level >20 ng/dl had a significantly higher risk of developing CRPC. Maximum testosterone levels ≥ 50 ng/dl (23% of patients) were associated with a significantly higher rate of progression to CRPC as compared to patients with maximum testosterone <20 ng/dl (27%) and patients with nadir testosterone levels ≥ 50 ng/dl (1%) had a significantly higher risk of dying from disease as

compared to patients with nadir testosterone 20–50 (21%) and <20 ng/dl (78%).

By contrast, there have been only two prospective studies on the additional benefit of suppressing testosterone to lower serum thresholds or minimum levels: In 32 patients followed up for about 2 years, time to CRPC was significantly longer in those with 9-month testosterone <32 ng/dl as compared to those with >32 ng/dl; however no additional predictive value was found for those <20 ng/dl [4]. In the second study, 153 patients with advanced PC were treated with GnRH agonists for 65 months. Testosterone levels <20 ng/dl after 6 months were found to be associated with a significantly lower risk of death and a trend towards a lower risk of disease progression ($P = 0.12$) as compared to those >20 ng/dl [19].

In conclusion, evidence is growing that sustainable testosterone suppression <20 ng/dl is beneficial in patients with PC. Reassuringly, this is widely achieved with all triptorelin SR formulations. Still, regular assessment of testosterone levels should be routine clinical practice for men on ADT and patients who under GnRH therapy do not succeed in achieving an appropriate testosterone suppression may qualify for an alternative method of ADT. Well-designed and sufficiently powered prospective studies using accurate and reliable testosterone assays are warranted to further evaluate the clinical benefit of a more rigorous testosterone suppression to minimum levels and to establish a new target threshold for testosterone levels.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The data sets generated during and/or analysed during the current study are not publicly available but may be made available by the corresponding author on reasonable request.

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