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Clinical Outcomes and Testosterone Levels Following Continuous Androgen Deprivation in Patients with Relapsing or Locally Advanced Prostate Cancer: A Post Hoc Analysis of the ICELAND Study

Bertrand Tombal,* Erik B. Cornel, Raj Persad, Anny Stari, Francisco Gómez Veiga, and Claude Schulman

From the Cliniques Universitaires Saint-Luc, Brussels, Belgium (BT), Ziekenhuisgroep Twente, Department of Urology, Hengelo, the Netherlands (EC), University Hospitals Bristol NHS Foundation Trust, Department of Urology, Bristol, UK (RP), Astellas Pharma Medical Affairs EMEA, Chertsey, UK (AS), Salamanca University Hospital and Translational Research Group of Urology GITUR-IBSAL, Salamanca, Spain (FGV), and Clinic E Cavell and University of Brussels, Brussels, Belgium (CS)

*Correspondence: Institut de Recherche Clinique, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium (telephone: +32 2 7645540; Fax: +32 2 7645580; E-mail: bertrand.tombal@uclouvain.be).

Other author emails: E.Cornel@zgt.nl; rajpersad@bristolurology.com; anny.stari@astellas.com; fgveiga@telefonica.net; profschulman@outlook.com

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ABSTRACT

Purpose: Lower serum testosterone levels correlate with improved cause-specific survival and longer time to progression in the first year of continuous androgen deprivation in men with prostate cancer. ICELAND was a large, European study demonstrating the efficacy of leuprorelin (Eligard®) during continuous androgen deprivation. This post hoc analysis investigated serum testosterone levels within the first year of continuous androgen deprivation for survival and time to progression.

Materials and Methods: In ICELAND (NCT00378690), patients with locally advanced/relapsing non-metastatic prostate cancer, with prostate-specific antigen levels ≤1 ng/mL following a 6-month induction with leuprorelin 3-month depot 22.5 mg (plus bicalutamide 50 mg/day for 1 month), were randomized 1:1 to continuous androgen deprivation (n=361) or intermittent androgen deprivation (n=340) with leuprorelin for 36 months. Patients receiving continuous androgen deprivation were stratified by minimum, median, and maximum testosterone levels during the first year of therapy into ≤20, >20 to ≤50, and >50 ng/dL subgroups. Cause-specific survival and time to prostate-specific antigen (castrate-resistant prostate cancer) progression were analyzed.

Results: A total of 90.1%, 83.5%, and 74.5% of patients receiving continuous androgen deprivation achieved minimum, median, and maximum serum testosterone levels of ≤20 ng/dL, respectively. Cause-specific survival rates and time to prostate-specific antigen progression did not differ between testosterone subgroups.

Conclusions: In patients receiving continuous androgen deprivation, cause-specific survival and time to prostate-specific antigen progression did not differ according to testosterone levels in the first year of therapy. This finding may be, in part, due to the induction period and effectiveness of leuprorelin in lowering testosterone.

INTRODUCTION

ADT is the standard systemic therapy in the management of advanced prostate cancer[1,2] and is often undertaken using long-acting LHRH analogs, with the aim of suppressing serum testosterone to castrate levels and inducing regression of the disease. For registration purposes, testosterone levels of ≤50 ng/dL are considered castrate level, but recent European Association of Urology and American Urological Association guidelines recognize testosterone levels of <20 ng/dL as the castration level of testosterone.[1,2]

A goal of ADT is to quickly lower and maintain testosterone levels below castrate level. Treatment of prostate cancer patients with LHRH agonists results in a diverse testosterone response often dependent on the agent, with serum levels typically ranging from ≤20 ng/dL to ≥50 ng/dL.[3] Additionally, breakthrough testosterone levels of >50 ng/dL occur in as many as 13% of patients.[3] A post hoc analysis of the PR-7 trial, comparing CAD and IAD in prostate cancer patients treated with a variety of LHRH agonists, was performed to address the clinical significance of these observations. Achievement of low nadir serum testosterone (≤20 ng/dL) within the first year of ADT correlated with improved CSS and time to PSA (CRPC) progression versus a nadir serum testosterone of >20 ng/dL.[4]

Leuprorelin (Eligard®) has been found to effectively lower testosterone, reducing PSA levels, in previous clinical trials.[5,6] ICELAND was a large, multicenter, European study demonstrating similar efficacy, tolerability, and quality of life with CAD and IAD with leuprorelin in non-metastatic prostate cancer.[7] This post hoc analysis of the CAD arm of the ICELAND trial was undertaken to repeat the post hoc analysis of the PR-7 trial, stratifying patients by testosterone

levels in the first year after randomization to determine if low testosterone levels correlated with improved CSS and time to PSA (CRPC) progression.

MATERIALS AND METHODS

The ICELAND study was a 42-month, phase IIIb, open-label, randomized, multicenter study that recruited patients from 102 centers in 20 European countries. Full methods are detailed in the primary manuscript,[7] with inclusion and exclusion criteria in the Supplementary.

Study Design

Patients were treated with leuprorelin acetate 22.5 mg 3-month depot for 6 months and received bicalutamide 50 mg once daily for 1 month from the first injection with leuprorelin acetate. Two successive PSA levels ≤1 ng/mL (≥2 weeks apart) after 6 months were required for patients to proceed to randomization.

The randomized phase ran from visit 4 (month 6) to visit 16 (month 42). Patients were randomly assigned 1:1 to either CAD or IAD with leuprorelin acetate 22.5 mg 3-month depot. Treatment was stopped 36 months after randomization, and patient follow-up was at 6-month intervals for 18 months. Study visit timing and end points are outlined in the Supplementary (including Supplementary Table 1). The first patient's first visit was in March 2006; the final patient's last visit was in April 2013.

Post Hoc and Statistical Analysis

Patients receiving CAD therapy were stratified by minimum, median, and maximum testosterone levels achieved into ≤20 ng/dL (≤0.7 nmol/L), >20 to ≤50 ng/dL (>0.7 to ≤1.7 nmol/L), and

>50 ng/dL (>1.7 nmol/L) subgroups. Pre-dose serum testosterone measurement was mandated every 3 months. Testosterone was centrally measured using the Elecsys® electrochemiluminescent immunoassay (Roche, CH). The limit of detection was 2.5 ng/dL, the limit of quantitation was 12.0 ng/ml, and the measuring range was 2.5–1500 ng/dL.[8] Data were collected during the first year of therapy from the date of randomization. CSS and time to PSA (CRPC) progression were analyzed by Kaplan-Meier analyses and Cox proportional hazards regression models. CSS was a post hoc end point, defined as the time from randomization to the date of death resulting from prostate cancer or a complication of cancer treatment to match the end point in the Klotz et al post hoc analysis.[4]

Time to PSA progression was defined as castrate serum testosterone <50 ng/dL plus either biochemical progression (defined as three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir with PSA >2 ng/mL) or radiological progression (defined as the appearance of ≥2 new bone lesions on bone scan or enlargement of a soft tissue lesion using Response Evaluation Criteria in Solid Tumors). HR with the Wald 95% CI computed by a Cox proportional hazards regression model was calculated, comparing the rate of hazard in the testosterone subgroup ≤20 ng/dL (≤0.7 nmol/L) with the other >20 to ≤50 ng/dL (>0.7 to ≤1.7 nmol/L) and >50 ng/dL (>1.7 nmol/L) subgroups.

RESULTS

A total of 1131 patients were screened for the ICELAND study, of whom 933 entered the induction phase. Of these, 701 patients were randomized and 232 patients discontinued before randomization. The main reasons for discontinuation after screening, but before randomization, were “not fulfilling the in- or exclusion criteria” (n = 176; 18.9%), “other” (n = 22; 2.4%), and

"consent withdrawal" (n=13; 1.4%). At the last visit prior to randomization, 137 of the 144 available PSA measurements of the subjects that were subsequently not randomized were ≥1 ng/mL. Only 2.8% (10/354) of the available PSA measurements at that visit were ≥1 ng/mL for the CAD group and 2.1% (7/335) for the IAD group. A total of 361 patients were assigned to CAD (Figure 1). This post hoc analysis included 345 eligible patients in the CAD arm, 339 of whom developed CRPC. Patient demographics were presented in the primary publication of the ICELAND study.[7]

During the first year of randomized leuprorelin treatment, less than 3% of patients were included in any of the highest testosterone-level subgroups (>50 ng/dL [>1.7 nmol/L]) [Table 1]. The minimum testosterone level of >50 ng/dL (>1.7 nmol/L) was reported in 0.3% of patients, and the median and maximum testosterone levels of >50 ng/dL (>1.7 nmol/L) were reported in 0.9% and 2.9% of patients, respectively. Minimum, median, and maximum testosterone levels of ≤20 ng/dL (≤0.7 nmol/L) were achieved in the majority of patients [90.1%, 83.5%, and 74.5%, respectively].

There was no significant difference among the three testosterone subgroups in time to CSS (Table 2; Figure 2). Patients who did not achieve a minimum testosterone of ≤20 ng/dL (≤0.7 nmol/L) did not have a shorter time to CSS, with an estimated HR of 0.89 (95% CI 0.4–1.8). Time to CSS was not reached in patients with minimum serum testosterone of >50 ng/dL (>1.7 nmol/L). Similarly, patients with median testosterone of >20 ng/dL (>0.7 nmol/L) had no difference in time to CSS compared with patients with median testosterone of ≤20 ng/dL (≤0.7 nmol/L) [>20 to ≤50 ng/dL (>0.7 to ≤1.7 nmol/L): HR 0.84; 95% CI 0.4–1.6; >50 ng/dL (>1.7 nmol/L): HR 2.74; 95% CI 0.2–12.7]. Furthermore, patients with a maximum testosterone

level ≤20 ng/dL (≤0.7 nmol/L) did not differ significantly in time to CSS compared with those patients with serum testosterone between 20 and 50 ng/dL (>0.7 to ≤1.7 nmol/L) or >50 ng/dL (>1.7 nmol/L), with an estimated HR of 1.13 (95% CI 0.6–1.9) and 3.59 (95% CI 0.9–10.0), respectively.

There was also no significant difference among the three testosterone subgroups in time to PSA (CRPC) progression (Table 2; Figure 3). Patients who did not achieve a minimum testosterone ≤20 ng/dL (≤0.7 nmol/L) did not have a higher risk of developing CRPC, with an estimated HR of 5.06 (95% CI 1.3–16.1). Time to PSA (CRPC) progression was not reached in patients with minimum serum testosterone >50 ng/dL (>1.7 nmol/L). Similarly, patients with median testosterone of >20 to ≤5 ng/dL (>0.7 to ≤1.7 nmol/L) had no difference in time to PSA (CRPC) progression compared with those patients with median serum testosterone ≤20 ng/dL (≤0.7 nmol/L) [HR 3.92; 95% CI 1.2–12.3]. Time to CRPC was not reached in patients with median serum testosterone >50 ng/dL (>1.7 nmol/L). Furthermore, patients with a maximum testosterone level of >20 ng/dL did not differ significantly in PSA (CRPC) progression compared with those patients with serum testosterone between 20 and 50 ng/dL (>0.7 to ≤1.7 nmol/L) or >50 ng/dL (>1.7 nmol/L), with an estimated HR of 2.79 (95% CI 0.8–9.3) and HR of 4.57 (95% CI 0.2–26.8), respectively.

DISCUSSION

This post hoc analysis of the CAD arm of the ICELAND study investigating the relationship between testosterone levels within the first year after randomization to leuprorelin and time to progression and disease-specific survival found no difference in clinical outcomes between the subgroups. This is in contrast with the post hoc analysis of the PR-7 study, in which low nadir

serum testosterone (≤20 ng/dL) within the first year of ADT correlated with improved CSS and time to CRPC in men being treated for biochemical failure undergoing CAD. Two earlier retrospective studies also suggested that low testosterone levels achieved by ADT in the first year correlate with time to CRPC,[9,10] while other retrospective studies suggested a prognostic role for testosterone levels[11] and a correlation with risk of death[12] in patients receiving ADT.

Findings in this analysis may be due, at least in part, to the effectiveness of leuprorelin in lowering testosterone levels, as only one patient had a minimum testosterone level of >50 ng/dL (>1.7 nmol/L) and ten patients had a maximum testosterone level of >50 ng/dL (>1.7 nmol/L). In addition, testosterone was measured using an electrochemiluminescence immunoassay, a common testosterone assay routinely used in clinical practice, ensuring the testosterone data presented are clinically relevant. Furthermore, a range of LHRH agonist preparations (buserelin, goserelin, leuprolide as subcutaneous or intramuscular injection, and leuprorelin as intramuscular or subcutaneous injection with varying doses and administration schedules) or bilateral orchiectomy was acceptable in the PR-7 trial,[4] while only leuprorelin Atrigel® depot (Eligard®) as 22.5 mg 3-month subcutaneous depot injections was used in the ICELAND study.[7] This may help account for the differing numbers of patients in each testosterone subgroup between the PR-7, Perachino et al (2010), Bertaglia et al (2013) studies, and the ICELAND study. Furthermore, patients in an earlier study by Oefelein et al (2000) underwent bilateral orchiectomy,[10] while patients in the Morote et al (2007) study received 3-month depots of LHRH agonist every 90 days, with a subset contininuing treatment with bicalutamide.[9] In addition, patients in the Perachino et al (2010) study were treated with 10.8 mg goserelin every 12 weeks,[12] while patients in the Bertaglia et al (2013) study received a long-acting formulation of commercially available LHRH agonist every 3 months with concomitant bicalutamide during the first 4 weeks

to prevent tumor flare.[11] These differences demonstrate the range of LHRH agonist agents used in studies that have investigated the relationship between testosterone levels and clinical outcomes in prostate cancer. The performance of these various LHRH agonist formulations in relationship with the pharmacologic performance of Eligard® has been discussed previously.[13]

Additionally, differences between the PR-7 and ICELAND study designs may contribute to the dissimilar results. While stratification of patients was performed using testosterone levels obtained 0 to 12 months following treatment initialization in the PR-7 trial, stratification in the ICELAND study was performed 6 to 18 months following treatment initialization. If the first year testosterone levels after the initialization of CAD are critical to the prognostic value of clinical outcome, the ICELAND post hoc analysis may have been compromised by excluding the first 6 months from the analysis.

Another notable difference was that eligible patients in PR-7 were required to have a rising PSA level >3 ng/mL that was higher than the post-radiation therapy nadir, whereas eligible patients in ICELAND were required to have a serum PSA of ≥0.4 ng/mL that had risen on three successive occasions. At baseline, 20% of the randomized ICELAND patients had a PSA of <2.5 ng/mL. Patients with lower PSA values have lower Gleason scores, smaller tumors, and lower tumor-recurrence rates. In the PR-7 trial, 99.9% of patients had a baseline PSA of >3 ng/mL.[14] Thus, patients in the PR-7 trial were more likely to experience disease recurrence. Additionally, in the ICELAND study patients were excluded from the randomized treatment period if they did not demonstrate two successive serum PSA levels of ≤1 ng/mL (at least 2 weeks apart) after 6 months of ADT. Prior to randomization, 95% of the available PSA measurements for subjects that were subsequently not randomized were ≥1 ng/mL. In contrast, only 2.8% of the CAD and

2.1% of the IAD available PSA measurements at that visit were ≥1 ng/mL. However, patients not responding to hormonal treatment in the PR-7 trial were not excluded from the analysis. Hormonally unresponsive patients would have a poorer clinical outcome, and the ICELAND post hoc analysis may have been further compromised by excluding this group.

Further differences, which may have impacted the results observed in this study, include the baseline characteristics of patients and cohort size. As this was a post hoc analysis, the minimum number of patients in each of the different testosterone subgroups was not predefined and thus the current analysis was not powered to detect differences between these groups in the outcomes presented here. In particular, the number of patients receiving local treatment was probably greater in the ICELAND study, as this was an inclusion criterion but was not in PR-7. Also, in the PR-7 study, baseline PSA and Gleason score >7 correlated with time to CRPC, whereas age, Gleason score, and baseline PSA correlated with CSS. However, in the current study, this was not investigated. As such, the impact of castration levels of testosterone on the development of CRPC and CSS remains controversial and further investigation is required. Additionally, CAD consisted of either orchiectomy or chemical castration with an LHRH in PR-7, whereas CAD only consisted of leuprorelin treatment in Iceland. As the number of patients who had orchiectomy in PR-7 is unknown, we cannot speculate as to the significance of this regarding the difference in the post hoc analyses for the two trials. Furthermore, cohort size differed in the PR-7 and ICELAND trials. Taken together with the lower risk of disease recurrence in the ICELAND study discussed above, these differences in cohort size may have further impacted this post hoc analysis of the ICELAND trial.

Notably, while no significant difference in clinical outcomes between testosterone subgroups was observed, which may partly have been due to fewer patients in the group with the highest testosterone levels in this study, a trend in the same direction as that seen in the PR-7 trial was observed when patients were stratified by minimum and median testosterone levels. Together with the limitations discussed earlier, these results suggest that while no significant difference was observed in this study, a larger sample size may help to overcome differences in testosterone subgroup sizes and show any relationships between testosterone levels and clinical outcomes.

CONCLUSIONS

In conclusion, this analysis of the ICELAND study demonstrated no differences in CSS and time to PSA (CRPC) progression among the ≤20 ng/dL (≤0.7 nmol/L), >20 to ≤50 ng/dL (>0.7 to ≤1.7 nmol/L), and >50 ng/dL (>1.7 nmol/L) testosterone-level subgroups in the CAD arm receiving leuprorelin treatment. These results contrast the PR-7 study post hoc analysis, and may be explained by differences in study design and patient population, as well as the effectiveness of leuprorelin treatment. Further studies are necessary to reach more definitive conclusions.

ACKNOWLEDGMENTS

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FIGURE LEGENDS

Figure 1. *Disposition of patients in the ICELAND study*

Figure 2. *Time to CSS according to the minimum (a), median (b), and maximum (c) testosterone levels in the first year of CAD*

Figure 3. *Time to PSA progression according to the minimum (a), median (b), and maximum (c) testosterone levels in the first year of CAD*

Table 1. *Distribution of minimum, median, and maximum testosterone levels during first year of CAD*

	Testosterone level, ng/dL		
	≤20	>20–≤50	>50
Minimum	311 (90.1%)	33 (9.6%)	1 (0.3%)
Median	288 (83.5%)	54 (15.7%)	3 (0.9%)
Maximum	257 (74.5%)	78 (22.6%)	10 (2.9%)

Table 2. *CSS and time to CRPC stratified by minimum, median, and maximum testosterone levels*

Testosterone level, ng/dL	N	Cause-specific survival			PSA (CRPC) progression		
		Median (95% CI)	HR (95% CI)	p value*	Percentage (95% CI)	HR (95% CI)	p value*
Minimum							
≤20	311	33 (33–34)	1		33 (NE)	1	
>20−≤50	33	33 (NE)	0.89 (0.4–1.8)	0.849	33 (NE)	5.06 (1.3–16.1)	0.062
>50	1	33 (NE)	NE		33 (NE)	NE	
Median							
≤20	288	33 (33–34)	1		33 (NE)	1	
>20−≤50	54	33 (NE)	0.84 (0.4–1.6)	0.598	33 (NE)	3.92 (1.2–12.3)	0.083
>50	3	33 (NE)	2.74 (0.2–12.7)		33 (NE)	NE	
Maximum							
≤20	257	33 (33–34)	1		33 (NE)	1	
>20−≤50	78	33 (NE)	1.13 (0.6–1.9)	0.196	33 (NE)	2.79 (0.8–9.3)	0.165
>50	10	32 (NE)	3.59 (0.9–10.0)		32 (NE)	4.57 (0.2–26.8)	

*Likelihood ratio test.

Supplementary

Inclusion and exclusion criteria

Men with locally advanced prostate cancer (T3−T4) or elevated or rising PSA levels (≥5 mg/mL) after radical prostatectomy or radiotherapy that had relapsing prostate cancer with a serum PSA of ≥0.4 ng/mL following radical prostatectomy and ≥1 ng/mL following radiotherapy that had risen on three successive occasions were screened. Inclusion criteria were age ≥18 and <80 years, Gleason score ≥6, Eastern Cooperative Oncology Group performance status of 0–2, and ≥5-year life expectancy. Patients were excluded if they had any other malignancy or metastatic disease, were receiving chemotherapy or other hormonal therapy, had testosterone levels ≤50 ng/dL (≤1.7 nmol/L), or had any condition that would preclude safe study completion. Patients underwent a rigorous assessment at screening, including TNM classification and a biopsy-based Gleason assessment. Radionuclide bone scan (technetium 99m-methylene diphosphonate bone scintigraphy) or a computed tomography scan of the abdomen and pelvis was also performed to exclude the presence of metastases. Patients provided written informed consent prior to study entry. The protocol was reviewed by the independent ethics committee/institutional review board at each study center.

Study end points

The primary end point was time to PSA progression, defined as three consecutive increasing PSA values ≥4 ng/mL at least 2 weeks apart during the randomized treatment period. Secondary efficacy end points included PSA progression-free survival, defined as time from randomization to either PSA progression or death; overall survival, defined as time from randomization to either the last available assessment or death, occurring no later than 60 months after randomization;

and time to serum testosterone >50 ng/dL (>1.7 nmol/L) [continuous androgen deprivation group only].

Efficacy data were analyzed for all patients who were randomized at visit 4 and treated. Time-to-event data were analyzed using the Kaplan-Meier method.

Figure 1

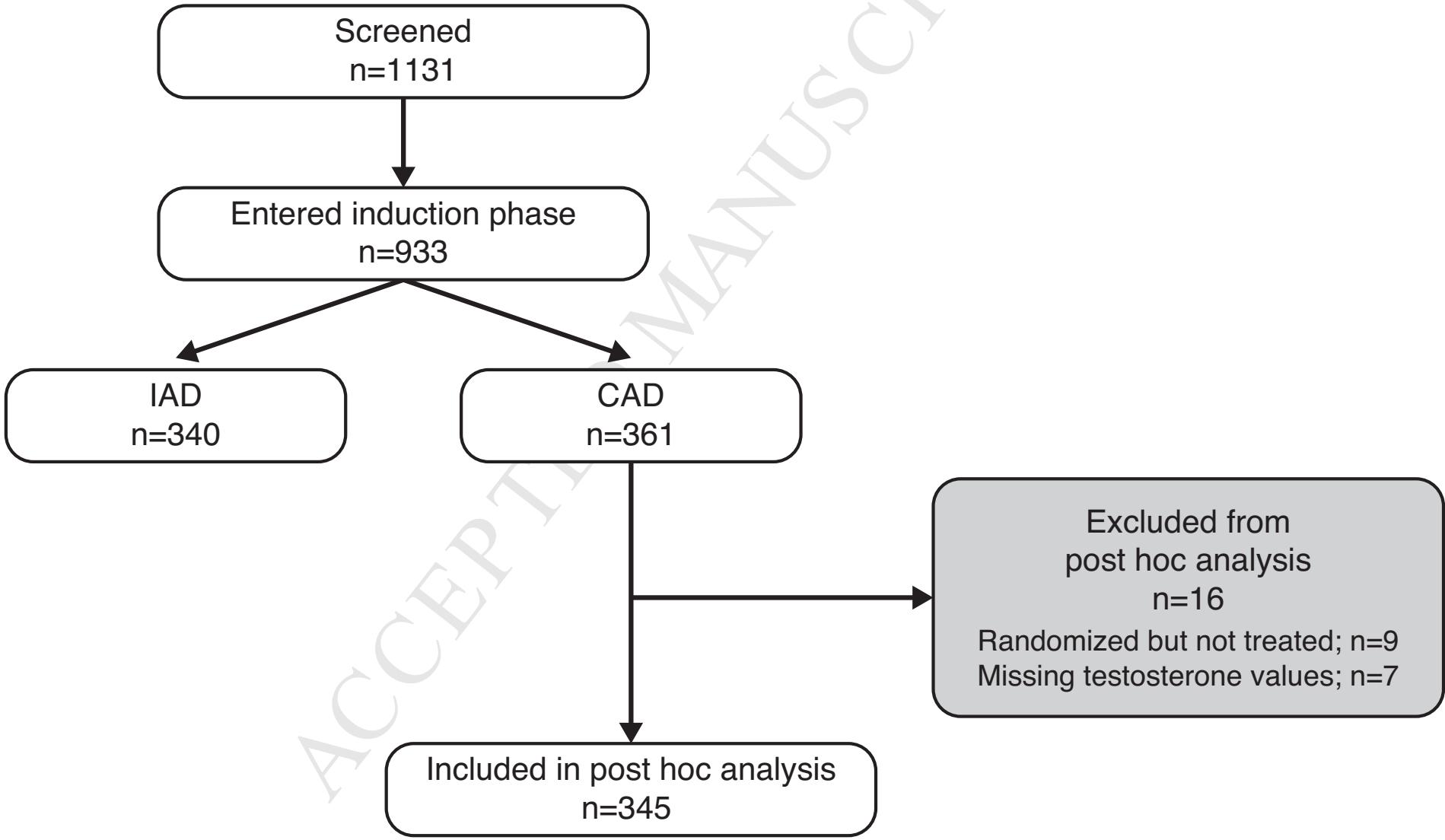
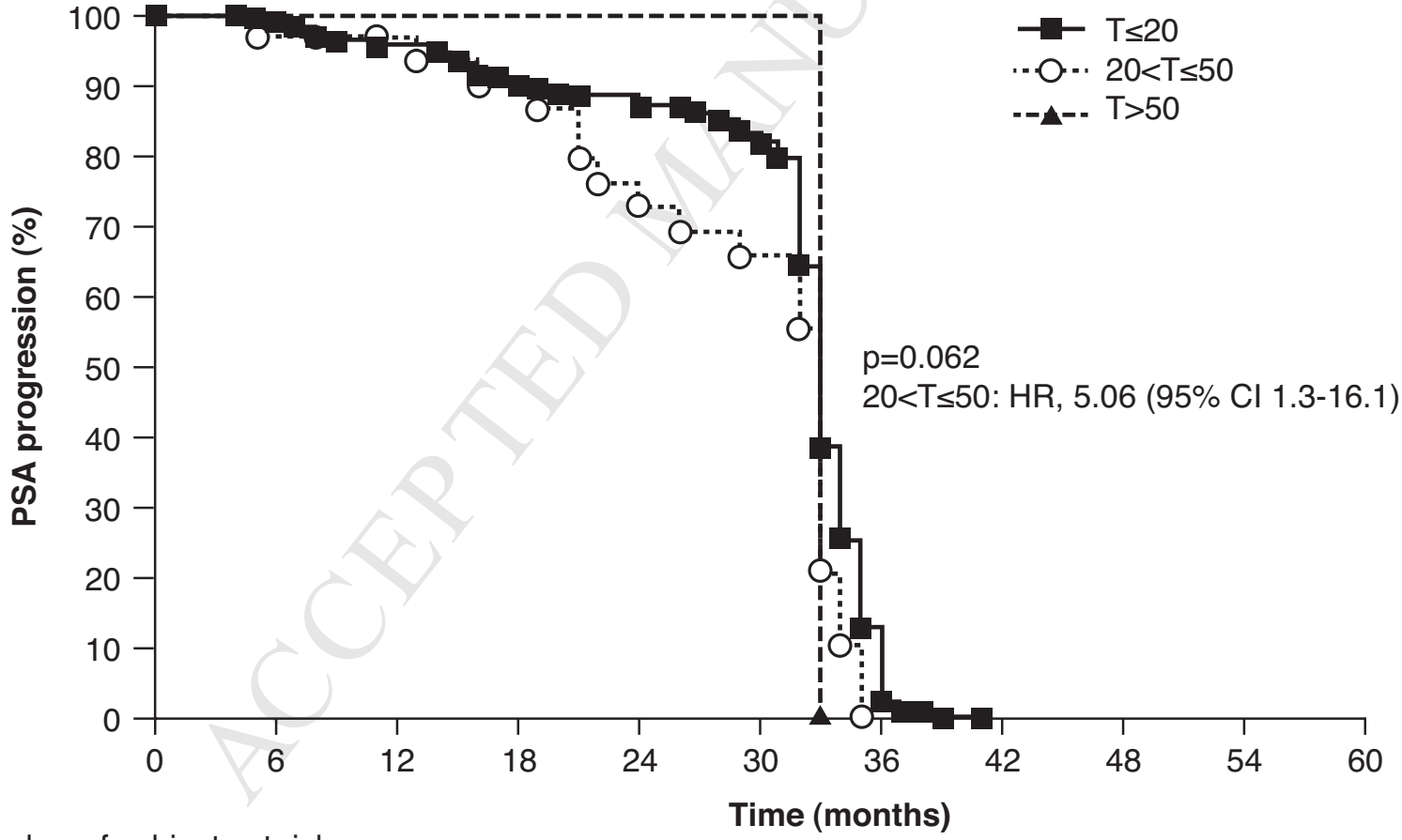


Figure 2a

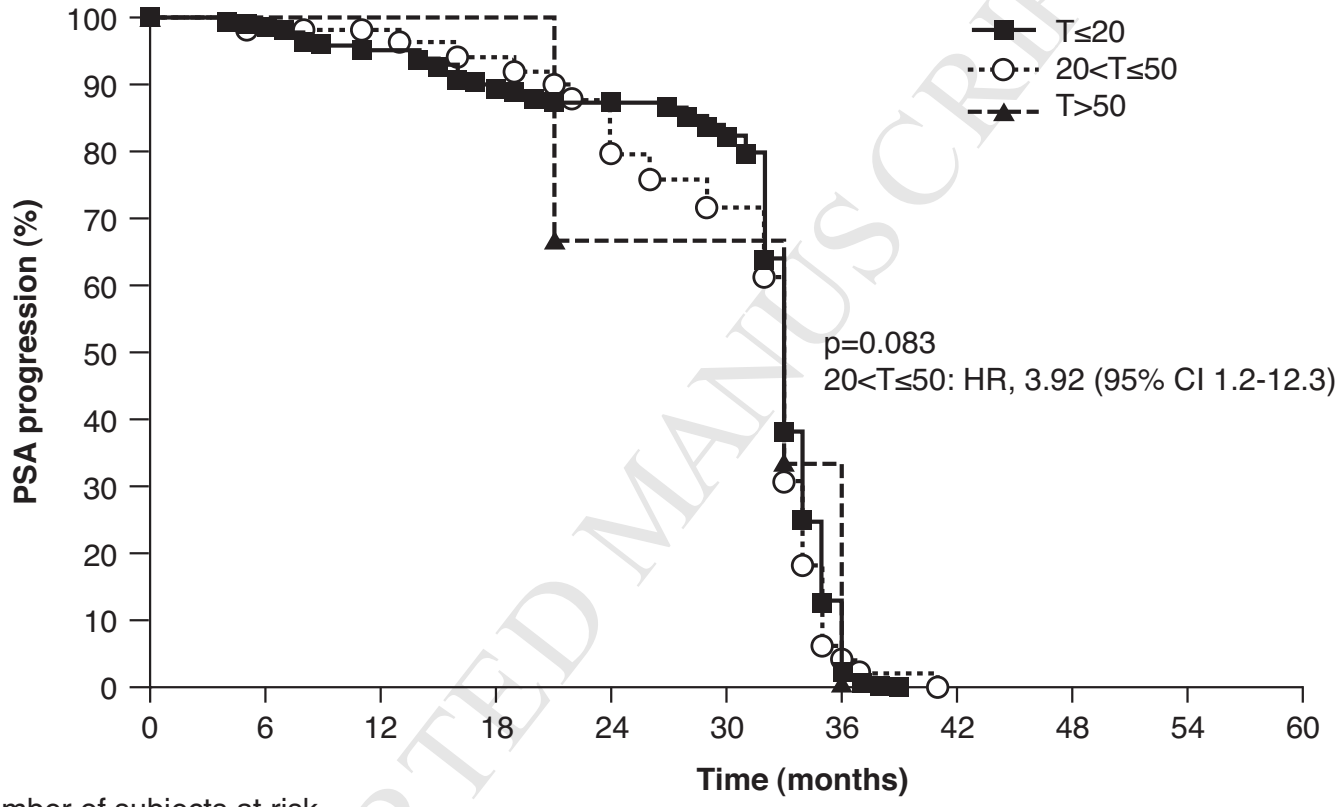
Figure 2a



Number of subjects at risk

T20	311	306	290	273	264	248	7	0	0	0	0
20<T50	33	30	28	26	21	19	0	0	0	0	0
T>50	1	1	1	1	1	1	0	0	0	0	0

Figure 2b

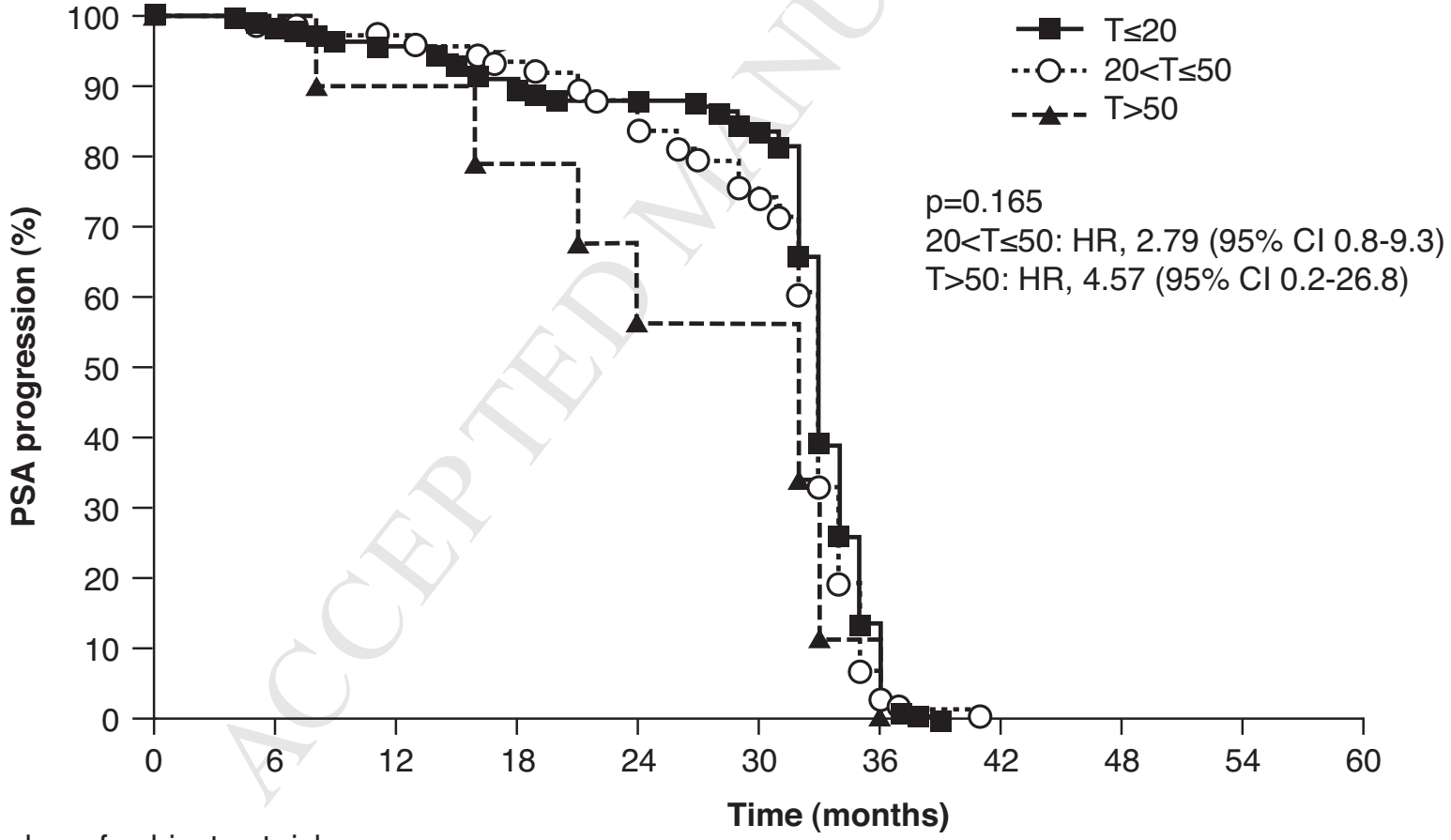


Number of subjects at risk

T20	288	283	268	251	245	231	5	0	0	0	0
20<T50	54	51	48	46	39	35	2	0	0	0	0
T>50	3	3	3	3	2	2	0	0	0	0	0

Figure 2c

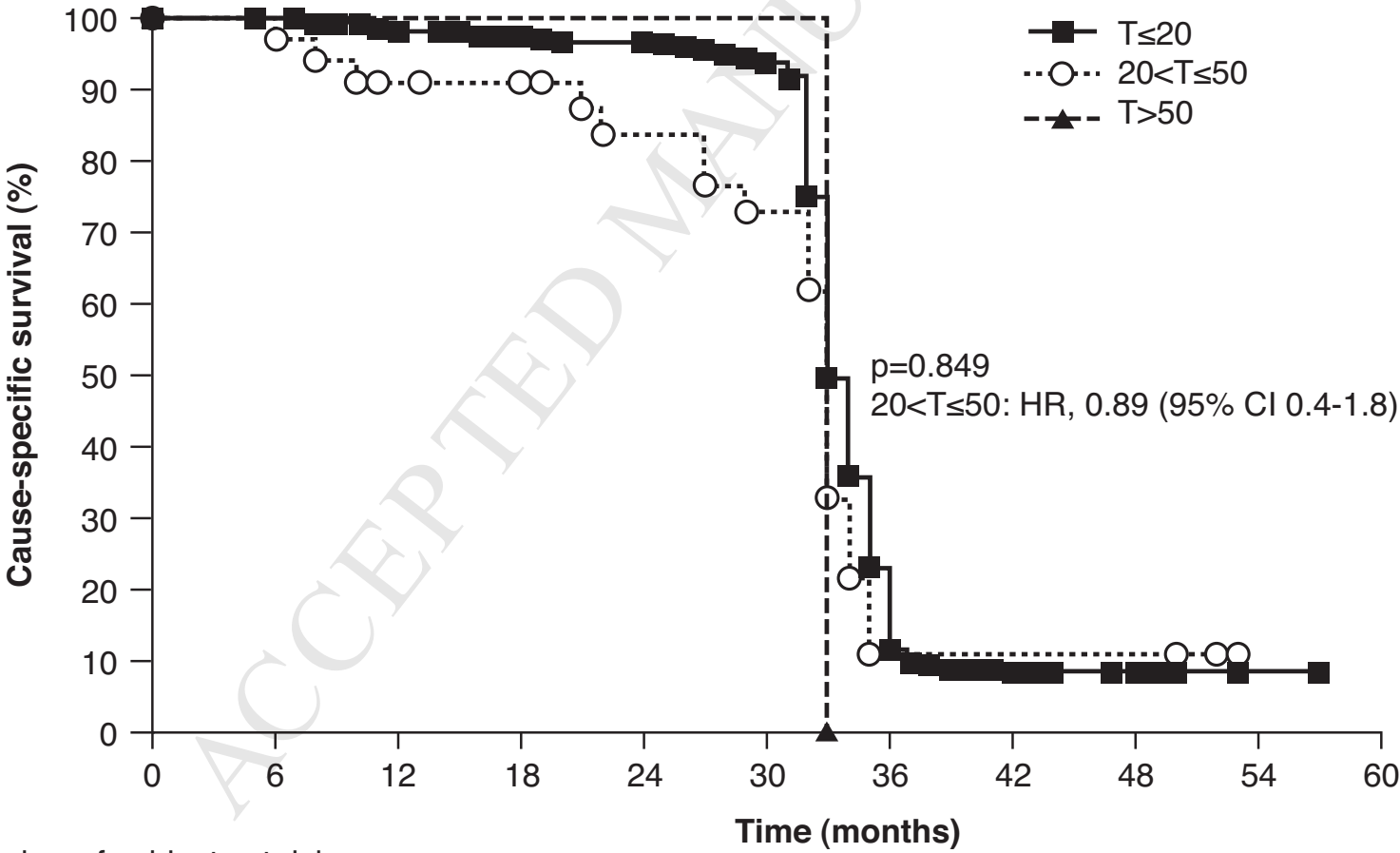
Figure 2c



Number of subjects at risk

T20	257	252	240	225	220	209	5	0	0	0	0
20<T50	78	75	71	68	61	54	2	0	0	0	0
T>50	10	10	8	7	5	5	0	0	0	0	0

Figure 3a

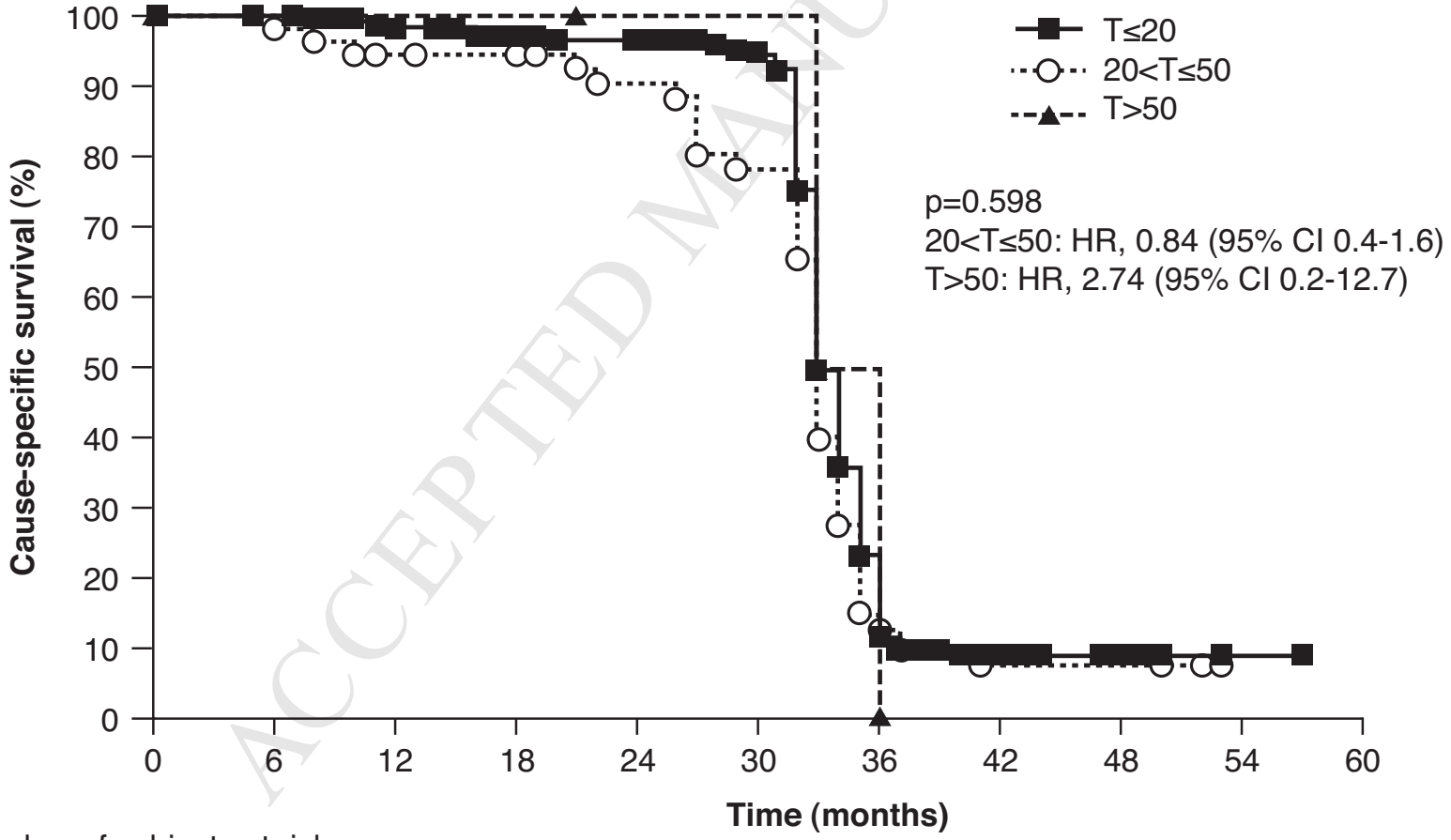


Number of subjects at risk

T20	311	310	297	287	279	263	30	12	6	1	0
20<T50	33	32	29	27	23	20	3	3	3	0	0
T>50	1	1	1	1	1	1	0	0	0	0	0

Figure 3b

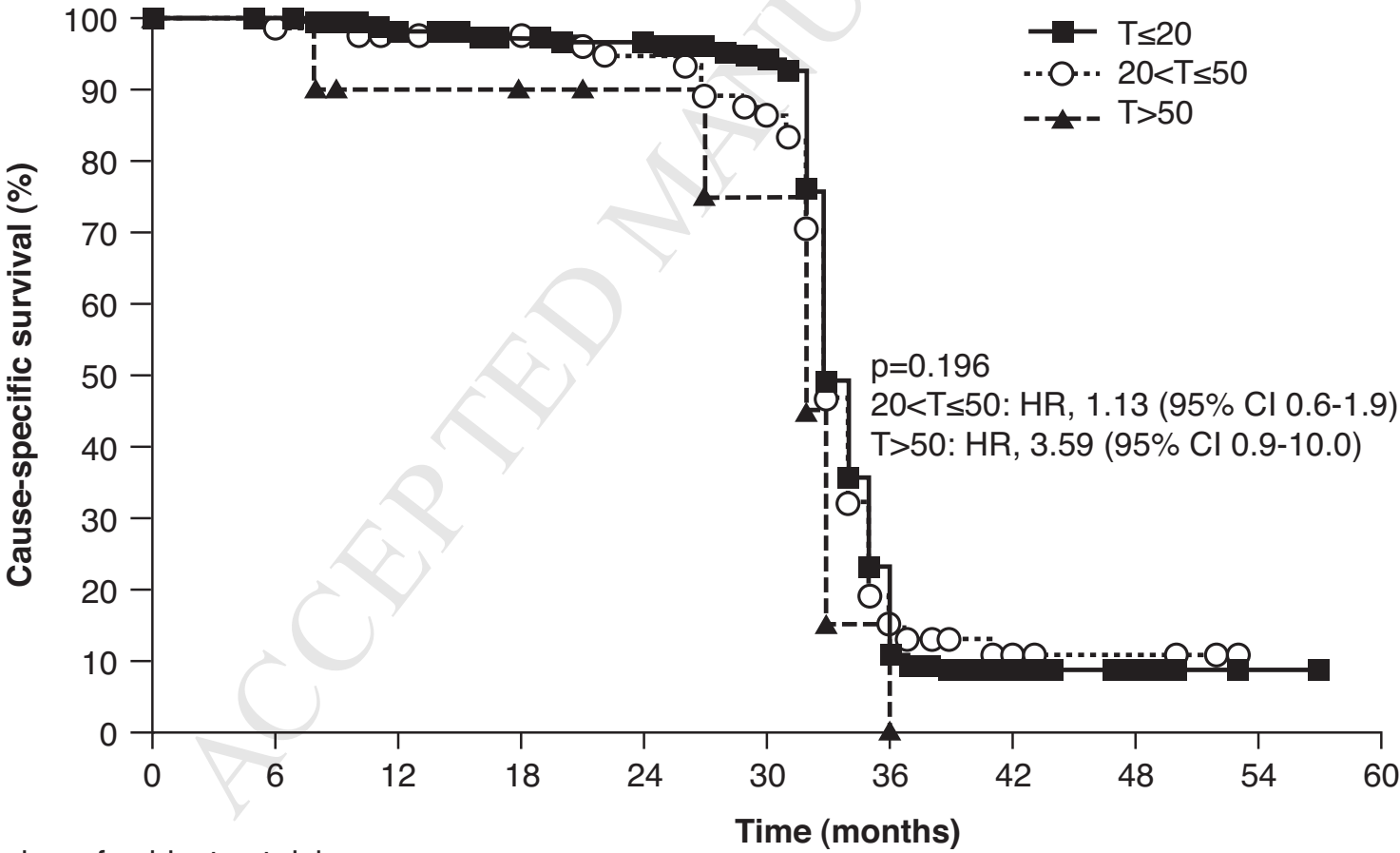
Figure 3b



Number of subjects at risk

T20	288	287	275	265	257	245	23	12	6	1	0
20<T50	54	53	49	47	44	37	5	3	3	0	0
T>50	3	3	3	3	2	2	0	0	0	0	0

Figure 3c



Number of subjects at risk

T20	257	256	246	237	229	219	24	11	6	1	0
20<T50	78	77	73	71	68	60	9	4	3	0	0
T>50	10	10	8	7	6	5	0	0	0	0	0

Supplementary Table 1. *Study visit timing*

	Screening visit	Induction phase			Randomized phase				Long-term follow-up
		Baseline	Month 3	Month 6	CAD		IAD		
Day/month	-21 to -7	0	3	6	9, 12, 15…	42	9, 12, 15…	42	48–60
Visit number	1	2	3	4	5, 6, 7…	16	5, 6, 7…	16	17–19
Leuprorelin 22.5 mg 3-month depot		Yes	Yes	Yes	Yes*		Yes†		
Bicalutamide 50 mg QD		Yes‡					Yes†		

*Leuprorelin 22.5 mg 3-month depots continuously in the continuous ADT group.

†Patients in the intermittent ADT group, following PSA levels reaching ≥2.5 ng/mL during the off-treatment phase, commenced leuprorelin 22.5 mg 3-month depot + bicalutamide (50 mg QD) for 1 month from the time of first leuprorelin depot injection.

‡All patients received bicalutamide (50 mg QD) for 1 month starting from the time of first leuprorelin depot injection.

ADT = androgen deprivation therapy; CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen; QD = once daily.

Abbreviations and Acronyms

ADT = androgen deprivation therapy

CAD = continuous androgen deprivation

CI = confidence interval

CRPC = castration-resistant prostate cancer

CSS = cause-specific survival

HR = hazard ratio

IAD = intermittent androgen deprivation

LHRH = luteinizing hormone-releasing hormone

NE = not estimable

PSA = prostate-specific antigen