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Prostate Cancer

Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND)

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Abstract

Background: Intermittent androgen deprivation (IAD) has received increasing attention; however, the current literature is still limited, especially in nonmetastatic prostate cancer (PCa), and the relative efficacy and safety benefits of IAD versus continuous androgen deprivation (CAD) remain unclear.

Objective: To add to the knowledge base regarding efficacy and potential benefits, including reduced side effects and improved quality of life (QoL), of IAD versus CAD in patients with nonmetastatic relapsing or locally advanced PCa.

Design, setting, and participants: A 42-mo phase 3b open-label randomised study in 933 patients from 20 European countries.

Intervention: Following a 6-mo induction with leuporelin acetate (Eligard) 22.5 mg 3-mo depot, patients were randomised to CAD or IAD with leuporelin for 36 mo.

Outcome measurements and statistical analysis: The primary end point was time to prostate-specific antigen (PSA) progression while receiving luteinising hormone-releasing hormone agonist, defined as three consecutive increasing PSA values ≥ 4 ng/ml ≥ 2 wk apart. Secondary end points included PSA progression-free survival (PFS), overall survival (OS), testosterone levels, performance status, and QoL.

Results and limitations: A total of 933 patients entered the induction phase; 701 were randomised. The median number of injections administered after randomisation was 12 (range: 1–12) for the CAD group and 3 (range: 1–10) for the IAD group. There were no statistically significant or clinically relevant differences between the groups for time to PSA progression, PSA PFS, OS, mean PSA levels over time, or QoL. A similar number of adverse events was observed in each group; the most common were hot flushes and hypertension. Study limitations include the open-label design and absence of formal testosterone recovery assessment.

Conclusions: IAD and CAD demonstrated similar efficacy, tolerability, and QoL in men with non-metastatic PCa. The principal benefit of IAD compared with CAD is a potential cost reduction with comparable OS rates. There are no apparent QoL benefits.

Patient summary: This randomised trial showed that both intermittent and continuous hormone therapy had similar efficacy, tolerability, and quality-of-life profiles in patients with relapsing M0 or locally advanced prostate cancer. Intermittent therapy may be a valid option for selected patients.

Trial registration: ClinicalTrials.gov identifier NCT00378690.

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1. Introduction

It has long been recognised that continuous androgen deprivation (CAD) therapy in patients with prostate cancer (PCa) can induce side effects such as decreased libido, impotence, decreased lean body mass, increased fat mass, increased insulin resistance, and osteoporosis [1]. These effects can significantly alter quality of life (QoL), especially in younger men. One alternative approach to CAD, recommended by the European Association of Urology (EAU) [2] and the National Institute of Health and Care Excellence [3], is intermittent androgen deprivation (IAD) therapy, during which androgen deprivation therapy (ADT) is discontinued once prostate-specific antigen (PSA) levels fall below a certain level and is restarted when PSA levels begin to rise [4]. The 2015 EAU guidelines suggest that IAD can be offered to a range of patients with PCa after a standardised induction period of ADT [2], providing they are willing and able to comply with the strict follow-up (and clinical examinations) necessitated by this treatment approach.

Although the concept of IAD is not new [5], the literature still largely fails to answer the question of the relative benefits of IAD versus CAD, especially in nonmetastatic patients. Recent studies conclude that IAD is noninferior to CAD in terms of overall survival (OS), although one study in patients with metastatic disease showed small OS benefits with IAD [6] and was equivalent to CAD for cancer control. Findings are less clear regarding prevention of long-term effects of ADT and QoL outcomes [4,7–9]; however, previous studies were heterogeneous in design, study populations, and treatment schedules.

As such, the ICELAND study, conducted in 20 European countries, aimed to add to the knowledge base regarding the efficacy and safety profile of IAD compared with CAD, focusing on a nonmetastatic population treated with the luteinising hormone-releasing hormone (LHRH) analogue leuprorelin acetate 3-mo depot, which has not been widely evaluated in the context of IAD.

2. Patients and methods

2.1. Design and procedures

This was a 42-mo phase 3b open-label randomised multicentre study, recruiting patients from 102 centres in 20 European countries (Supplementary Table 1). Men with locally advanced PCa (T3–T4) or elevated or rising PSA levels (≥ 5 mg/ml) after radical prostatectomy (RP) or radiotherapy were screened. Inclusion criteria were age ≥ 18 and < 80 yr, Gleason score ≥ 6 , Eastern Cooperative Oncology Group (ECOG) performance status score 0–2, and ≥ 5 -yr life expectancy. Patients were excluded if they had any other malignancy or metastatic disease, were receiving chemotherapy or other hormonal therapy, had testosterone levels ≤ 1.7 nmol/l or 50 ng/dl, 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 centre.

2.1.1. Treatment

The induction treatment phase ran from screening (visit 1) to randomisation (visit 4). Patients were treated with leuprorelin acetate (Eligard; Astellas Pharma Inc., Northbrook, IL, USA) 22.5 mg 3-mo depot for 6 mo and received bicalutamide (Casodex; AstraZenica, London, UK) 50 mg once daily for 1 mo from the first injection. PSA determinations were made up to 2 wk before each visit so the result was available to the investigator at the visit. Two successive PSA levels ≤ 1 ng/ml (≥ 2 wk apart) after 6 mo were required for patients to proceed to randomisation.

The randomised phase ran from visit 4 (month 6) to visit 16 (month 42). Patients were randomly assigned to either CAD or IAD with leuprorelin acetate 22.5 mg 3-mo depot. Patients randomised to IAD had ADT discontinued immediately after randomisation and entered the first off-treatment phase. If the patient's serum PSA level rose to ≥ 2.5 ng/ml, independent of testosterone level, treatment was restarted every 3 mo (plus bicalutamide 50 mg for 1 mo) until PSA declined to ≤ 1 ng/ml (on two successive occasions ≥ 2 wk apart). Both CAD and IAD were stopped 36 mo after randomisation, and patient follow-up was at 6-mo intervals for 18 mo. Study visit timing is outlined in Supplementary Figure 1. The first patient's first visit was in March 2006; the final patient's last visit was in April 2013.

2.1.2. Primary end point

The primary end point was time to PSA progression, defined as three consecutive increasing PSA values ≥ 4 ng/ml at least 2 wk apart while receiving leuprorelin.

2.1.3. Secondary end points

Secondary efficacy end points included PSA progression-free survival (PFS), defined as time from randomisation to either PSA progression or death; OS, defined as time from randomisation to either the last available assessment or death, occurring no later than 60 mo after randomisation; time to serum testosterone > 50 ng/dl or 1.7 nmol/l (CAD group only); World Health Organization (WHO)/ECOG performance status (5-point scale); and health-related QoL, measured by EORTC QLQ-C30 and PCa-specific module QLQ-PR25.

Testosterone levels and testosterone breakthrough (defined as time to serum testosterone > 50 ng/dl or 1.7 nmol/l [conventional] or > 20 ng/dl or 0.7 nmol/l [conservative]) were assessed at each visit. EORTC QLQ-C30 and QLQ-PR25 questionnaires [10,11] were completed at visits 2–16 and at early withdrawal.

2.1.4. Safety

Reported adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v.3.0.

2.1.5. Power calculations and statistical analyses

With 350 randomised patients per arm, it was calculated that the study would provide 90% power to demonstrate superiority on the primary end point at the final analysis (3 yr after randomisation) if the proportion of patients with PSA progression at 3 yr was 38.9% in the CAD arm, based on previous estimates [12], and $< 27.3\%$ or $> 51.2\%$ in the IAD arm.

Efficacy, safety, and tolerability data were analysed for all patients who were randomised at visit 4 and treated. Time-to-event data were analysed using the Kaplan-Meier method.

3. Results

Of 1131 screened patients, 933 entered the induction phase (Fig. 1). There were no relevant differences between

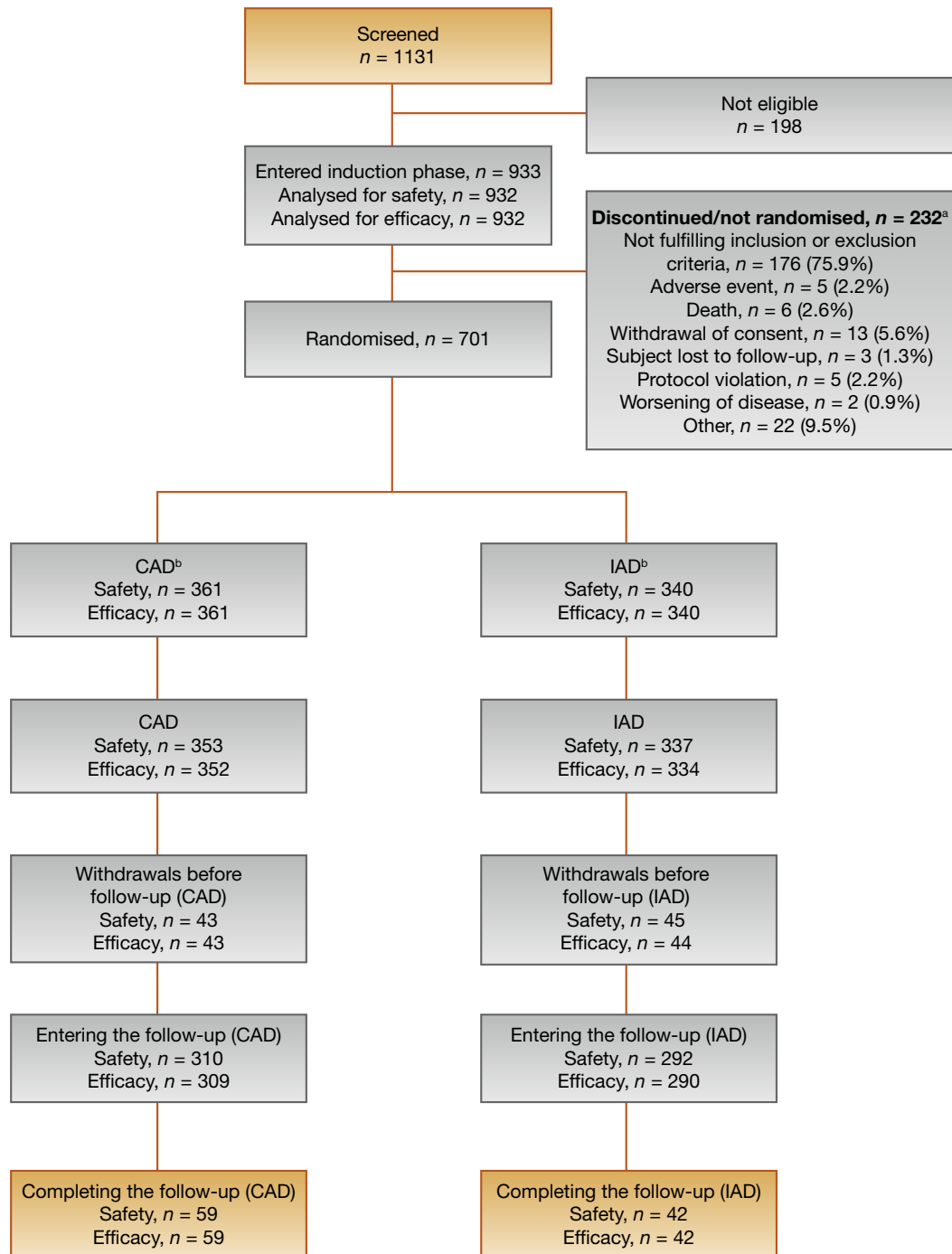


Fig. 1 – Disposition of patients.

^a There is a discrepancy in the nonrandomised group due to a patient who was not documented as a screening failure, although he should have been, based on the fact that one of the inclusion criteria was not met (locally advanced but TNM classification was missing); no leuprolide acetate was administered.

^b Population additionally included patients who were not randomised.

CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation.

treatment groups for baseline disease characteristics or comorbidities (Table 1).

During induction, median testosterone levels for all patients decreased from 397 ng/dl (13.8 nmol/l) to 11.0 ng/dl (0.4 nmol/l) at month 3, with a further small decline at month 6. Median PSA levels decreased from 8.6 ng/ml to 0.20 ng/ml at month 3 and remained at this level at month 6.

Overall, 701 patients were randomised (Fig. 1), of whom 58% had locally advanced disease, 26.7% had relapsing PCA following RP, and 15.3% had relapsing PCA following other therapies. A total of 131 patients (19.1%) withdrew after randomisation: 70 in the CAD group and 61 in the IAD group. Supplementary Table 2 details the primary reasons for study withdrawal.

Table 1 – Baseline disease characteristics and comorbidity profile

	CAD (n = 361)	IAD (n = 340)	Not randomised (n = 231)	Total (n = 932)	p value
Indications for ADT, n (%)					0.534 ^a
Locally advanced PCa	211 (59.9)	187 (56.0)	NA	NA	
Relapsing PCa following RP	88 (25.0)	95 (28.4)	NA	NA	
Relapsing PCa following other therapies	53 (15.1)	52 (15.6)	NA	NA	
Time since diagnosis, d, median (range)	74 (0–4401)	88 (0–4185)	43 (0–5470)	66 (0–5470)	0.544 ^b
Prior therapy, n (%)					
Any surgery	120 (33.2)	115 (33.8)	35 (15.2)	270 (29.0)	0.870 ^a
Any radiation	60 (16.6)	66 (19.4)	30 (13.0)	156 (16.7)	0.336 ^a
Any chemotherapy	0	3 (0.9)	1 (0.4)	4 (0.4)	0.114 ^c
Any other therapy	56 (15.5)	55 (16.2)	24 (10.4)	135 (14.5)	0.810 ^a
Gleason score, n (%)					0.752 ^a
≤6	142 (39.7)	127 (37.7)	72 (31.2)	341 (36.8)	
7	134 (37.4)	125 (37.1)	85 (36.8)	344 (37.1)	
≥8	82 (22.9)	85 (25.2)	74 (32.0)	241 (26.0)	
Missing ^d	3	3	0	6	
T, n (%)					0.082 ^c
T0–2	64 (9.1)	78 (11.7)	25 (5.5)	167 (9.2)	
T3–4	284 (40.6)	254 (38.3)	204 (44.5)	742 (40.7)	
TX	4 (0.6)	0	0	4 (0.2)	
Missing ^d	9	8	2	19	
Comorbidities of interest, n (%)					
Hypertension	194 (53.7)	173 (50.9)	118 (51.1)	485 (52.0)	0.449 ^a
Hypercholesterolaemia	47 (13.0)	61 (17.9)	17 (7.4)	125 (13.4)	0.071 ^a
Diabetes mellitus	33 (9.1)	39 (11.5)	17 (7.4)	89 (9.5)	0.310 ^a
Myocardial ischaemia	35 (9.7)	45 (13.2)	36 (15.6)	116 (12.4)	0.141 ^a

ADT = androgen deprivation therapy; CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; NA = not applicable; PCa = prostate cancer; RP = radical prostatectomy.

^a Chi-square test.

^b Log rank test.

^c Fisher exact test.

^d Missing patients not included in percentage calculations.

3.1. Description of intermittent androgen deprivation cycles

The median number of IAD injections administered during the randomised phase was 3 (range: 1–10) compared with 12 (range: 1–12) for the CAD group, with a mean duration of 327 d and 89 d between injections for the IAD and CAD groups, respectively. Of patients receiving IAD, 36%, 22%, and 16% did not need to reinitiate ADT at months 12, 24, and 36, respectively. In the IAD group, 184 patients received 1–3 injections, 76 received 4–6 injections, 8 received 7–9 injections, and 5 received 10–12 injections.

The mean testosterone level at randomisation was 11.4 ng/dl (0.4 nmol/l) for the IAD group. Mean testosterone levels subsequently increased (range: 61.0–268.0 ng/dl [2.1–9.3 nmol/l]), and at 36 mo (visit 16) mean testosterone was 174.3 ng/dl (6 nmol/l).

3.2. Primary end point

Time to PSA progression did not statistically differ between treatment groups ($p = 0.718$), with a similar number of events recorded in each group (34 for CAD and 30 for IAD) (Fig. 2) at 36 mo. Median time to PSA progression was not reached. Estimated 3-yr PSA progression rate percentage was 10.6 (95% confidence interval [CI], 7.7–14.6) and 10.1 (95% CI, 7.1–14.2) for CAD and IAD, respectively. Similar results were observed when the analysis was stratified by primary diagnosis.

3.3. Secondary end points

PSA PFS did not differ significantly ($p = 0.865$) between the CAD and IAD groups (43 vs 41 events) (Supplementary Fig. 2); estimated 3-yr PSA PFS percentage was 13.2 (95% CI, 10.0–17.5) and 13.1 (95% CI, 9.7–17.5) for CAD and IAD, respectively. There was a steep decrease in mean PSA levels by the end of the induction phase in both groups that was maintained through to visit 16 (Fig. 3).

Overall, 86 men died within 5 yr of study entry (44 in the CAD group and 42 in the IAD group) with no difference in OS between groups ($p = 0.969$) (Fig. 4). The estimated 5-yr OS percentage was 85.0 (95% CI, 80.0–88.8) and 81.8 (95% CI, 74.7–87.2) for CAD and IAD, respectively; this difference was not statistically significant.

Most CAD patients maintained castrate levels of testosterone throughout treatment (values remained between 9.0 and 12.9 ng/dl [0.3 and 0.5 nmol/l]), with breakthrough events occurring in 22 patients (6.3%). Time to conventional testosterone breakthrough during CAD is shown in Supplementary Figure 3.

3.4. World Health Organization/Eastern Cooperative Oncology Group performance status

The patients' WHO/ECOG status tended to deteriorate toward the end of the treatment period, with no notable differences between treatment groups.

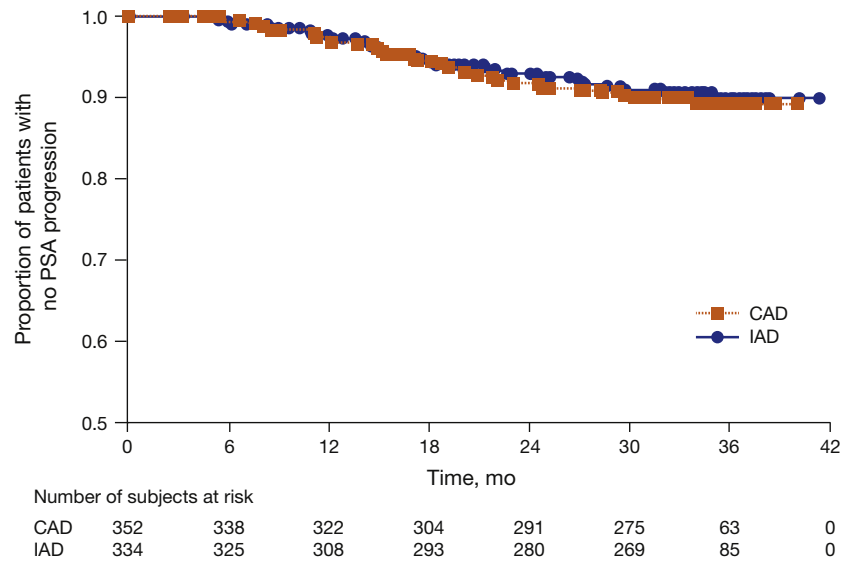


Fig. 2 – Kaplan-Meier plot for time to prostate-specific antigen progression.
CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen.

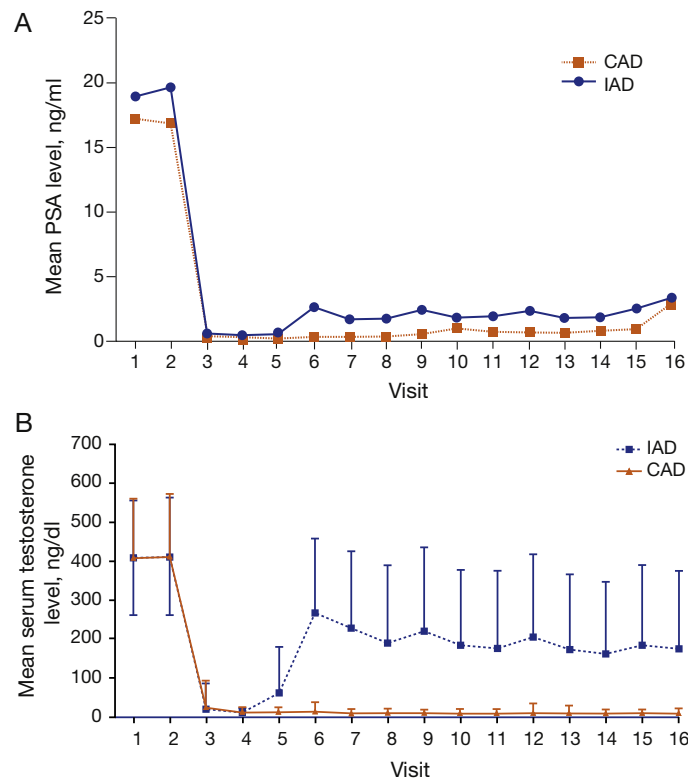


Fig. 3 – (A) Mean prostate-specific antigen levels at each visit; (B) mean (standard deviation) testosterone levels at each visit.
CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; PSA = prostate-specific antigen.

3.5. Quality of life

QoL using EORTC QLQ-C30 was comparable for the IAD and CAD groups (Supplementary Table 3). For the functional scales, the mean scores were all >80 with no notable changes during the randomised phase. Mean

global health status scores decreased slightly during the randomised phase, with no notable differences between groups. Nausea, vomiting, and appetite loss were the most distressing symptoms reported. Additional QoL data are reported in Supplement 1 and Supplementary Table 4.

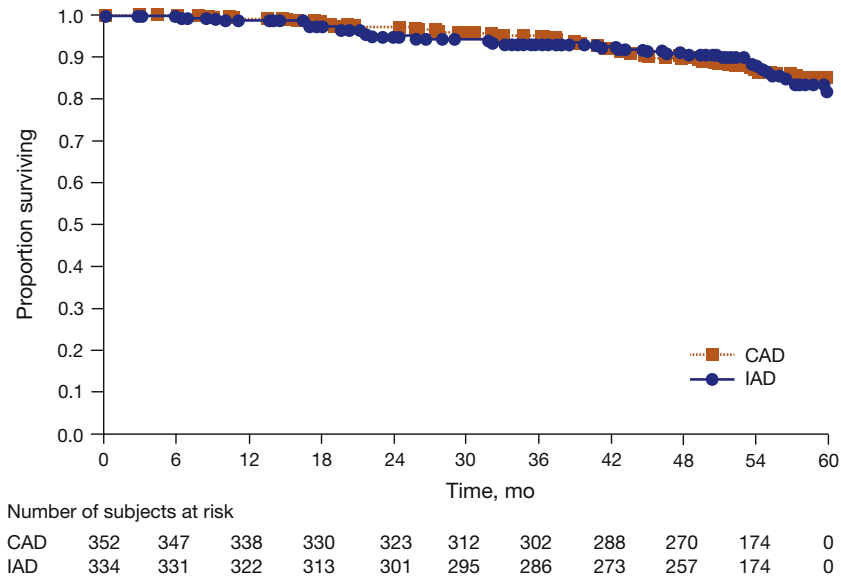


Fig. 4 – Kaplan-Meier plots for time to overall survival.
CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation.

3.6. Toxicity and adverse events

During the randomised phase, 510 patients (73.9%) had one AE or more, with no clinically relevant difference between groups (Table 2). Overall, 178 patients (25.8%) had one or

more serious AEs. The most common AEs were hot flushes, hypertension, and constipation (Table 2); most were grade 1 (mild) or grade 2 (moderate). Supplementary Table 5 shows the AEs occurring in ≥2% of patients during the randomised phase. Forty-two patients (6.1%) discontinued randomised

Table 2 – Summary of adverse events and treatment-related adverse events (randomised phase)^a

	CAD (n = 352)	IAD (n = 334)	Total (n = 686)	p value
Patients with any TEAE, n (%)	256 (72.5)	254 (75.4)	510 (73.9)	0.394 ^b
Patients with TEAE by severity, n (%)				0.966 ^b
Grade 1: mild	47 (13.3)	53 (15.7)	100 (14.5)	
Grade 2: moderate	109 (30.9)	107 (31.8)	216 (31.3)	
Grade 3: severe	73 (20.7)	63 (18.7)	136 (19.7)	
Grade 4: life threatening/disabling	17 (4.8)	16 (4.7)	33 (4.8)	
Grade 5: death	9 (2.5)	14 (4.2) ^c	23 (3.3)	
Missing	1 (0.3)	1 (0.3)	2 (0.3)	
Patients with treatment-related TEAEs ^d , n (%)	145 (41.1)	124 (36.8)	269 (39.0)	0.394 ^b
Patients with serious TEAEs, n (%)	88 (24.9)	90 (26.7)	178 (25.8)	0.594 ^b
Patients with treatment-related serious TEAEs ^d , n (%)	4 (1.1)	4 (1.2)	8 (1.2)	1.000 ^e
Deaths ^f , n (%)	9 (2.5)	15 (4.5)	24 (3.5)	0.173 ^b
Discontinued due to TEAE ^g , n (%)	17 (4.8)	25 (7.4)	42 (6.1)	0.153 ^b
Discontinued due to treatment-related TEAE ^{d,g} , n (%)	4 (1.1)	0	4 (0.6)	0.124 ^e
AEs of interest, n (%)				
Hot flushes	68 (19.3)	72 (21.4)	140 (20.3)	0.493 ^b
Hypertension	45 (12.7)	37 (11.0)	82 (11.9)	0.473 ^b
Constipation	21 (5.9)	23 (6.8)	44 (6.4)	0.638 ^b
Back pain	18 (5.1)	19 (5.6)	37 (5.4)	0.753 ^b
Fatigue	17 (4.8)	15 (4.5)	32 (4.6)	0.820 ^b

AE = adverse event; CAD = continuous androgen deprivation; IAD = intermittent androgen deprivation; TEAE = treatment-emergent adverse event.

^a Study population includes patients who were randomised and for whom postrandomisation safety data were available.

^b Chi-square test.

^c One patient died, but the cause of death was not recorded as a grade 5 AE.

^d AEs that are possibly or probably treatment related or for which the relationship is missing.

^e Fisher exact test.

^f Only AEs with outcome “fatal” are counted.

^g Only AEs that were the primary reason for discontinuation are taken into account.

treatment due to AEs. Analysis of AEs in patients with locally advanced versus relapsing PCa at baseline revealed no differences between CAD and IAD regarding number of AEs, serious AEs, or AEs leading to drug discontinuation. Twenty-four patients (3.5%) died during randomised treatment; no deaths were deemed related to treatment.

4. Discussion

In this large multicentre randomised study of IAD and CAD in patients with relapsing MO after RP or radiotherapy or locally advanced PCa, there were no statistically significant or clinically relevant differences between groups for any time-to-event end points (time to PSA progression, PSA PFS, or OS) or mean PSA levels over time. Results were seen in the context of considerably fewer injections in the IAD than CAD group (median: 3 for IAD and 12 for CAD). However, there were no apparent differences in performance status, QoL, or treatment tolerability between groups; both treatment strategies were similarly well tolerated, and most drug-related (and non-drug-related) AEs were mild to moderate.

A number of previously published studies have compared CAD and IAD, many in samples of <500 patients [4,6–9,12–20], but only one phase 3 study has been conducted in a purely nonmetastatic population [13]. Crook et al compared IAD with CAD in a large patient group that previously received primary or salvage radiotherapy for localised PCa [13]. IAD was found to be noninferior to CAD with respect to OS (median: 8.8 vs 9.1 yr). All other studies comparing IAD with CAD included either a mix of patients with metastatic and nonmetastatic disease, or only patients with metastatic disease. Some of these have shown better QoL or improvement in individual side effects among those treated with IAD compared with CAD [14,17]. A recent open-label study assessing IAD with a LHRH antagonist in 213 patients of varying disease stage observed improved sexual functioning and fewer AEs during the off-treatment period [21].

Benefits of IAD on sexual functioning and AEs were also confirmed in a recent meta-analysis of 13 trials composed of 6419 patients with hormone-sensitive PCa [8]. Although these findings are generally positive, it has been suggested that such benefits are at best modest and may depend on off-treatment period length and time to recovery of testosterone levels [7]. Taken together, these studies fail to provide consistent support for the theoretical IAD benefits, although they suggest there is no disadvantage to this approach either.

In our study, PSA progression in the CAD arm was markedly lower than reported in the study by de Leval et al on which our power assumptions were based, although the small sample size and different population in that study ($n = 33$ in the CAD group) could at least partly explain the difference [12].

IAD requires fewer drug doses, potentially leading to cost savings [4,22]. Although drug administration costs are likely to be lower for IAD, it should be noted that this approach requires strict follow-up monitoring, resulting in costs not associated with CAD that would need to be balanced against any absolute cost reductions from decreased drug use.

Strengths of this study are its large sample size, multiple objective outcome measures, and the exclusively nonmetastatic disease population. Our study, which adds to the small number of well-powered comparative studies in this patient population, is the first industry-sponsored study of its kind. We recognise that the treatment approach for the patients in the ICELAND study may have been different if conducted today; however, at the time of study initiation (2006), the options presented to patients were in line with typical practice and accepted guidelines. The primary study limitations are the open-label design and absence of formal assessment of testosterone recovery. We also acknowledge that PSA progression, as used in our study, is not a recognised surrogate end point for efficacy. It is, however, a modest end point for objective response and is strongly associated with OS [23]. Furthermore, the other outcomes used in the ICELAND study, namely PFS and OS, are of major clinical interest. Taken together, these end points provide appropriate data to contribute meaningfully to the knowledge base on IAD versus CAD.

5. Conclusions

In this open-label trial, IAD and CAD administered after a 6-mo induction with leuporelin acetate 22.5 mg 3-mo depot demonstrated comparable efficacy, tolerability, and QoL in patients with nonmetastatic locally advanced or relapsing PCa. The principal potential benefits of IAD compared with CAD include reduced drug acquisition costs with comparable OS rates. There were no apparent differences in QoL benefits between the treatment groups.

Author contributions: Claude Schulman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tombal, Schulman, Cornel, Baskin-Bey.

Acquisition of data: Schulman, Cornel, Matveev, Tammela, Schraml, Bensadoun, Warnack, Persad, Salagierski, Gómez Veiga, Baskin-Bey, López, Tombal.

Analysis and interpretation of data: López, Schulman, Cornel, Matveev, Tammela, Schraml, Bensadoun, Warnack, Persad, Salagierski, Gómez Veiga, Baskin-Bey, Tombal.

Drafting of the manuscript: Schulman, Cornel, Matveev, Tammela, Schraml, Bensadoun, Warnack, Persad, Salagierski, Gómez Veiga, Baskin-Bey, López, Tombal.

Critical revision of the manuscript for important intellectual content: Schulman, Cornel, Matveev, Tammela, Schraml, Bensadoun, Warnack, Persad, Salagierski, Gómez Veiga, Baskin-Bey, López, Tombal.

Statistical analysis: López.

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Other (specify): None.

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had a consulting relationship with Astellas between 2005 and 2008, although it does not constitute a current conflict of interest according to the International Committee of Medical Journal Editors guidelines. Teuvo L. Tammela is a study investigator for Astellas. Edwina Baskin-Bey was an employee of Astellas at the time of manuscript initiation. Beatriz López is an employee of Astellas. Bertrand Tombal is a paid adviser and study investigator for Astellas. Erik Cornel, Vsevolod Matveev, Jan Schraml, Henri Bensadoun, Wolfgang Warnack, Raj Persad, Marek Salagierski, and Francisco Gómez Veiga have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2015.10.007>.

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