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Review

Intermittent androgen deprivation therapy in patients with prostate cancer: Connecting the dots

Per-Anders Abrahamsson

Department of Urology, Skåne University Hospital, Lund University, Malmö, Sweden

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Abstract Intermittent androgen deprivation therapy (IADT) is now being increasingly opted by the treating physicians and patients with prostate cancer. The most common reason driving this is the availability of an off-treatment period to the patients that provides some relief from treatment-related side-effects, and reduced treatment costs. IADT may also delay the progression to castration-resistant prostate cancer. However, the use of IADT in the setting of prostate cancer has not been strongly substantiated by data from clinical trials. Multiple factors seem to contribute towards this inadequacy of supportive data for the use of IADT in patients with prostate cancer, e.g., population characteristics (both demographic and clinical), study design, treatment regimen, on- and off-treatment criteria, duration of active treatment, endpoints, and analysis. The present review article focuses on seven clinical trials that evaluated the efficacy of IADT *vs.* continuous androgen deprivation therapy for the treatment of prostate cancer. The results from these clinical trials have been discussed in light of the factors that may impact the treatment outcomes, especially the disease (tumor) burden. Based on evidence, potential candidate population for IADT has been suggested along with recommendations for the use of IADT in patients with prostate cancer.

1. Introduction

Intermittent androgen deprivation therapy (IADT) has found its way to clinics despite weak evidence of its clear superiority or non-inferiority over continuous androgen deprivation therapy (CADT). The main reasons for preferring IADT over CADT are reduced short- and long-term side-effects of androgen deprivation therapy (ADT) such as compromised sexual functioning, increased risk from cardiovascular diseases and diabetes, osteoporosis, loss of

E-mail address: Per-Anders.Abrahamsson@ferring.com.
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muscle mass, weight gain, cognitive decline, fatigue, depression, and hot flushes [1,2]. These side-effects tend to significantly impact the health-related quality of life (HRQoL) in patients undergoing CADT [3–7]. In addition, IADT offers an off-treatment period, which may provide a clinically meaningful relief from these side-effects, thereby improving the HRQoL and treatment compliance [8], and reducing the treatment costs. Most importantly, it is believed that IADT delays the progression to castration-resistant prostate cancer (CRPC), which is thought to begin early after treatment initiation [9,10]. However, stopping ADT prior to progression to CRPC should restore apoptotic potential and retain sensitivity to treatment re-initiation [11–13].

Data from phase 2 and phase 3 studies have shown that IADT may improve the tolerability of the treatment; however, the efficacy may be similar to CADT. Based on these findings, guidelines for the treatment of prostate cancer suggest that IADT may be no longer considered an experimental therapy [14]. Further, it is also noted that not all patients benefit from IADT [15]. Patients with non-metastatic cancer, without bone metastases, with cancer restricted to lymph nodes, and those with local or biochemical failure following radiotherapy are possibly good candidates for IADT [16,17]. On the other hand, patients with large tumors, multiple metastases, and prostate-specific antigen (PSA) levels >100 ng/mL do not have a good prognosis with IADT [18,19], mainly due to a shorter life expectancy and a shorter off-treatment period.

Considering the focus on IADT and data from published studies, it is important to understand different aspects of IADT, mainly, IADT regimen, patients who would benefit from IADT, and the factors governing treatment outcome. Other decision pointers could be the age and medical history of patient. However, studies done until now with IADT constitute mixed populations rather than pure cohorts (non-metastatic, metastatic, and locally advanced), and have variable study designs.

The present systematic review was undertaken to identify these aspects, and weigh the benefits and risks in patients with prostate cancer undergoing IADT. These aspects are discussed in the light of tumor burden, study design, study populations, study endpoints and their analyses, and guidelines for IADT issued by different societies (Table 1).

Table 1 IADT guidelines.

Guideline	Recommendation
AUA 2007 update	• IADT not being discussed
ASCO 2007 update	• More studies with longer follow-up and with larger patient cohorts are needed to determine the impact of IADT
EAU 2015	• IADT could maintain QoL in off-treatment periods and is significantly associated with lower treatment costs • IADT may provide an option for patients in metastatic stage
NCCN 2015	• IADT could reduce side-effects and may improve QoL, however, the benefits are unclear

IADT, intermittent androgen deprivation therapy; QoL, quality of life.

2. Methods

This systematic review includes seven studies, namely JPR.7, SEUG 9401, SEUG 9901, TAP 22, Finn Prostate, TULP, and SWOG 9346 [17,20–25]. All these are phase 3 studies that compared IADT with CADT. The eligibility criteria for studies to be included were a primary endpoint of survival or progression. Retrospective and single arm studies were not included. Besides these seven studies, there were few other studies comparing IADT and CADT for which we have listed the methods/results in Table 2 [16,26–34].

Data for median on- and off-treatment periods, post-treatment PSA levels (progression), overall survival (OS), progression-free survival, quality of life (QoL), adverse events (AEs), and testosterone recovery were presented here in a clear and consistent manner. The results were discussed after considering all the factors that may impact the treatment outcomes, especially the disease (tumor) burden. Based on evidence, potential candidate population for IADT was suggested and suitable recommendations for the use of IADT in patients with prostate cancer have been discussed.

3. Results

3.1. Study designs

Study design is the first challenge in IADT set-up, bringing in a large variability at the very first stage of conceptualization. A non-inferiority design is the best fit for comparing CADT with IADT, considering the ethical challenges with classical placebo-controlled trials in such patients. However, practically it is challenging as non-inferiority designs often require a larger sample size as compared with the superiority studies, putting a huge constraint on enrollment and execution of these studies. Another gap in non-inferiority studies is the lack of consensus on the non-inferiority margin for key outcomes, i.e., OS and progression-free survival.

Of the seven studies included in this review, three were non-inferiority studies (JPR.7 [17], SEUG 9901 [21], and SWOG 9346 [25]), and four were superiority studies (SEUG 9401 [20], Finn Prostate [23], TAP 22 [22], TULP [24]) and all studies compared CADT with IADT. All but one study included patients with metastatic or locally advanced prostate cancer (JPR.7 [17] included non-metastatic patients). All studies except TULP [24], TAP 22 [22], and SWOG 9346 [25] included mixed populations (Table 3).

The PSA eligibility criteria were 3–5 ng/mL for JPR.7 [17], SEUG studies [20,21], and SWOG 9346 [25]. For TAP22 [22], the PSA eligibility criterion was higher (>20 ng/mL), while it was variable in Finn Prostate study [23]. PSA criteria for TULP were not available in the publication [24]. The induction period was also quite variable in these studies: 3 months in SEUG studies [20,21], 6 months in TAP

Table 2 Summary of additional studies comparing intermittent androgen deprivation therapy (IADT) with continuous androgen deprivation therapy (CADT).

Study	Diagnosis	Study design	Treatment arms	Patients randomized, *n*	Regimen	PSA levels (ng/mL) (unless otherwise specified)		Follow-up (month)	Primary endpoint	Time to progression or progression rate	Cancer-specific survival	OS	Adverse events/QoL
						Cease treatment	Resume/ treatment						
Hering. 2000 [26]	Metastatic	Compare the efficacy	IADT	25	Induction only (10.5 months): CPA 200 mg/day orally	0.4	≥10 (initial ≤20) ± 50% initial (initial >20)	48 (median)	Time to progression and AEs	NR (IADT) *vs.* 20.1 months (CADT); NS	2 (8%) deaths	NR	Hormone resistance, impotence; Better QoL with IADT *vs.*CADT
			CADT	18	CPA 200 mg/day orally						2 (11.1%) deaths HR = 0.70 (0.09–5.44)		
de Leval. 2002 [16]	Locally advanced, metastatic or recurrent; hormone-naïve	Phase 3, randomized	IADT	35	Induction only (3–6 months): flutamide 250 mg, 3 times daily for 15 days; followed by flutamide and goserelin acetate (3.6 mg/month)	≤4	≥10	30.8 (mean)	Time to androgen independent prostate cancer	Time to progression or castration-resistant disease: 25.7 months (IADT) *vs.* 14.4 months (CADT); HR (95%) : 0.57 (0.07–4.64) Estimated 3-year progression rate: significantly lower in IADT (7%) *vs.* CADT (38.9%); $p = 0.0052$	2 (5.7%) deaths	NR	Hot flashes, loss of libido, and erectile dysfunction improved in men on IADT at least during off-treatment phase
			CADT	33	Goserelin + flutamide (250 mg orally every 8 h) without interruption						4 (12.1%) deaths HR = 0.46 (0.09–2.35)		
Schasfoort. 2003 [27]	Locally advanced or metastatic	NR	IADT	193	Buserelin + nilutamide	<4	≥20 (for metastatic); ≥10 (for locally advanced)	25 (median)	Time to progression	18 months	NA	Not reached while reporting	Hot flashes, erectile dysfunction, gynecomastia, liver dysfunction, and visual disturbance did not differ significantly between the groups
			CADT							24 months			
Miller. 2007 [28]	Locally advanced or metastatic	Compare the efficacy	IADT	335	Induction only (6 months): goserelin + bicalutamide	<4 or 90% initial level	NR	NR	Time to progression	16.6 months	NR	51.4 months	Sexual activity, pain, social functioning, emotional well-being, and vitality better with IADT; other AEs including cardiovascular events were similar
			CADT		Goserelin + bicalutamide					11.5 months; NS; HR (95%) : 0.69 (0.41–1.16)		53.8 months; NS; HR (95%CI): 1.04 (0.86–1.28)	
Irani. 2008 [29]	Locally advanced or metastatic	Compare the efficacy	IADT	67	Induction only (6 months): goserelin 10.8 mg 3-month depot and flutamide 250 mg 3 times daily and resumed 6 months later	6 months	6 months	60 (median)	Health related QoL, time to progression	HR (95%) : 1.1 (0.6–1.8) $p = 0.3$ favoring IADT	HR (95%) : 0.6 (0.2–1.6) $p = 0.12$ favoring CADT	HR (95%CI): 0.6 (0.3–1.3) $p = 0.06$ favoring CADT	No significant differences in QoL score between groups
			CADT	62	Goserelin and flutamide 250 mg 3 times daily continued without interruption								
Tunn. 2012 [30]	Recurrent (after prostatectomy)	Phase 3, randomized, prospective, non-inferiority	IADT	109	Induction only (6 months): goserelin 11.25 mg, 3-month depot, SC or IM + CPA 200 mg/day orally administered for the first 4 weeks to prevent tumor flare	≤0.5	≥3 or when clinical progression was observed	28 (median)	Androgen independent tumor progression	976 days	NR	NR	NR
			CADT	92	LHRHa					986 days; NS			

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Table 2 (*continued*)

Study	Diagnosis	Study design	Treatment arms	Patients randomized, *n*	Regimen	PSA levels (ng/mL) (unless otherwise specified)		Follow-up (month)	Primary endpoint	Time to progression or progression rate	Cancer-specific survival	OS	Adverse events/QoL
						Cease treatment	Resume/ treatment						
Verhagen. 2014 [31]	Asymptomatic metastatic	Open label, randomized	IADT CADT	131 127	Induction only (3–6 months): CPA 100 mg 3 times daily CPA 100 mg 3 times daily	Good or moderate response	PSA or clinical progression	NR	Time to PSA progression	NS	NS	NS	Physical and emotional function significantly better with IADT ($p < 0.05$). No observed difference between IADT and CADT for role and social function. Cognitive function significantly reduced in IADT 87% to baseline, 69% ($p < 0.05$)
Casas. 2016 [32]	Patients with biochemical failure after external beam radical radiotherapy	Non-inferiority, randomized, phase 3	IADT CADT	38 39	IADT (6 months) and CADT (36 months)	NR	NR	48 (median)	NR	No patient with risk of progression 3 with risk of progression	NR	NR	No significant differences in QoL score between groups
Schulman. 2016 [33]	Non-metastatic relapsing or locally advanced	Phase 3, open-label, randomized	IADT CADT	340 361	6 months induction with leuprorelin acetate 22.5 mg 3-month depot; Patients were randomized with leuprorelin for 36 months	≤1	≥2.5	18	Time to PSA progression	Time to PSA progression: $p = 0.718$ NS Estimated 3 years PSA progression comparable between IADT (10.1%) and CADT (10.6%); NS	NR	42 deaths 44 deaths $p = 0.969$; NS	QoL comparable between groups; Hot flushes, hypertension, constipation
Tsai. 2017 [34]	Advanced	Compared tolerability	IADT CADT	9772	Patients were either treated with IADT or CADT	NR	NR	54.6 (median)	AEs (serious toxicities)	NR	NR	NR	Lower risk of cardiovascular SAEs with IADT *vs.* CADT HR (95%CI): 0.64; (0.53–0.77); $p < 0.0001$

AE, adverse event; CADT, continuous androgen deprivation therapy; CI, confidence interval; CPA, cyproterone acetate; HR, hazard ratio; IADT, intermittent androgen deprivation therapy; IM, intra-muscular; ITT, intention to treat; LHRHa, luteinizing hormone releasing hormone agonist; NA, not applicable; NR, not reported; NS, non-significant; OS, overall survival; PSA, prostate-specific antigen; QoL, quality of life.

Table 3 Study design of studies comparing intermittent androgen deprivation therapy (IADT) with continuous androgen deprivation therapy (CADT).

Study	Study design	Patient population	PSA eligibility criteria (ng/mL)	Primary endpoint	Induction therapy	Induction treatment period (month)	PSA criteria for initiating off-treatment period (ng/mL)	PSA level to restart treatment (ng/mL)	Hazard ratio/ hypothesis	Assumed median survival/time to progression in CADT arm (year)
SEUG 9401 [20]	Superiority trial	Locally advanced or metastatic cancer	≥4 and <100	Progression-free survival	LHRH analogue + anti-androgen cyproterone acetate 200 mg/day	3	<4, or reduced by at least 80% of initial level by end of induction	≥10 for symptomatic patients and ≥20 for asymptomatic patients or PSA rose to ≥20% above nadir	0.70	6 (progression-free survival)
TULP [24]	NA	Metastatic cancer	NA	Progression-free survival	Busereline 6.6 mg (Suprefact), a 2-monthly subcutaneous depot, and oral nilutamide 300 mg (Anandron) (once a day for the first 4 weeks and 150 mg daily thereafter)	6	<4	M0 at baseline: ≥10; M1 at baseline: ≥20	NA	NA
Finn Prostate [23]	Superiority trial	Locally advanced or metastatic cancer	M1: any value; M0: ≥60; T3-4M0: ≥20	Progression-free survival	LHRH analogue goserelin acetate 3.6 mg subcutaneously every 28 days + cyproterone acetate 100 mg bid during first 12.5 days	6	<10, or by >50% if baseline PSA <20	>20 or above baseline	0.74	1.7 (progression-free survival)
JPR.7 [17]	Non-inferiority trial	Non-metastatic cancer; PSA relapse after radiotherapy	>3	Overall survival	LHRH agonist + non-steroidal anti-androgen	8	<4 and not more than 1 ng/mL above previous recorded value in that treatment cycle	>10	1.25	7 (overall survival)

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Table 3 (*continued*)

Study	Study design	Patient population	PSA eligibility criteria (ng/mL)	Primary endpoint	Induction therapy	Induction treatment period (month)	PSA criteria for initiating off-treatment period (ng/mL)	PSA level to restart treatment (ng/mL)	Hazard ratio/ hypothesis	Assumed median survival/time to progression in CADT arm (year)
TAP 22 [22]	Superiority trial	Metastatic cancer	>20	Overall survival	LHRH agonist leuprorelin sustained release 3.75 mg/ month + anti-androgen flutamide 250 mg tablet 3 times daily	6	<4	>10	0.51	2.5 (overall survival)
SEUG 9901 [21]	Non-inferiority trial	Locally advanced or metastatic cancer	≥4 and ≤ 100	Overall survival	LHRH agonist triptoreline 11.25 mg + anti-androgen cyproterone acetate 200 mg/day	3	<4	≥20	1.21	4.25 (overall survival)
SWOG 9346 [25]	Non-inferiority trial	Metastatic, hormone-sensitive cancer	>5	Overall survival	LHRH agonist + antiandrogen (goserelin and bicalutamide)	7	<4	>20, or Returned to baseline in patients who had PSA <20 before enrollment, or at investigator's discretion could be reinitiated when PSA >10 or symptoms developed	1.20	2.9 (overall survival)

LHRH, luteinizing hormone—releasing hormone; NA, not available/applicable; PSA, prostate-specific antigen.

22 [22], Finn Prostate [23], and TULP [24], 7 months in SWOG 9346 [25], and 8 months in JPR.7 [17]. There was some consensus regarding the PSA criteria for initiating the off-treatment period, i.e., for most of the studies, it was PSA levels <4 ng/mL, though in Finn Prostate [23], a higher cut-off (<10 ng/mL) was used. The PSA criteria to restart therapy varied from >10 ng/mL (JPR.7 [17], TAP 22 [22]) to >20 ng/mL (Finn Prostate [23], SEUG 9901 [21], SWOG 9346 [25]). In SEUG 9401, the criterion was different for symptomatic and asymptomatic patients (≥10 and ≥ 20 ng/mL, respectively) [20]. Similarly, in TULP it was different for M0 and M1 patients (≥10 and ≥ 20 ng/mL, respectively) [24]. The outcome measures included OS, time to disease progression (PSA levels) or progression-free survival, time to CRPC, and QoL in almost all of these studies (Table 3).

The follow-up durations also varied across studies (2.6—9.8 years, Table 4). However, it should be noted that a longer follow-up may be required in patients with less complicated disease and/or those with lower disease burden due to better life expectancy. It also means that this factor should be considered while making the assumptions with respect to survival endpoint trials as this subset of patients may have a slower progression-free survival and a better OS. Grouping together of patients with low and high disease burden may bias the overall results. Furthermore, non-cancer deaths, particularly those due to cardiovascular disease, maybe early deaths, and may again bias the OS results.

3.1.1. JPR.7

The treatment regimen for CADT included luteinizing hormone—releasing hormone (LHRH) agonist and an anti-androgen for a minimum of 4 weeks. IADT included the same induction treatment for 8 months, followed by an off-treatment period. Patients received up to nine treatment cycles.

Primary outcome measure was OS. Secondary outcome measures were the time to CRPC (three increases in the PSA level at least 1 month apart or evidence of new clinical disease while the patient was receiving ADT and serum testosterone at castrate levels), QoL using European Organization for Research and Treatment of Cancer QoL core questionnaire (EORTC QLQ-C30), duration of off-treatment periods, and time to testosterone and potency recovery [17].

3.1.2. SEUG studies

Patients received ADT with monthly depot injections of LHRH analogue and an anti-androgen for a minimum of 2 weeks preceding ADT. Patients achieving PSA cut-off 3 months after induction therapy were randomized to receive CADT (same as induction treatment) or IADT (induction followed by off-treatment period). Patients received up to two treatment cycles.

In SEUG 9401, primary outcome measure was time to subjective or objective progression. Secondary outcome measures were survival and QoL [20]. In SEUG 9901, primary outcome measure was OS. Secondary outcome measures included cause-specific survival, time to subjective or objective progression, and QoL [21]. Off-treatment period was also recorded in both the studies.

3.1.3. TAP 22

Patients received ADT with LHRH agonist and an anti-androgen. After 6 months of induction therapy, eligible patients were randomized to either CADT or IADT. In the IADT group, therapy was resumed for 3 consecutive months as soon as PSA increased to >10 ng/mL.

Primary outcome measure was OS after end-of-induction phase. Secondary outcome measures were progression-free survival and overall HRQoL [22].

3.1.4. Finn Prostate

Patients received LHRH analogue and an anti-androgen. Patients achieving PSA cut-off were randomized to CADT or IADT. In the IADT group, off-treatment period was followed by at least 24 weeks of ADT based on the PSA levels.

Primary outcome measure was time to progression. Secondary outcomes were OS, prostate cancer specific survival, and time to treatment failure. Other outcome measures were HRQoL [23].

3.1.5. TULP

Patients received ADT with LHRH agonist buserelin and an anti-androgen for minimum 4 weeks preceding ADT. Primary outcome measure was time to clinical progression. Secondary outcome measures were QoL, OS, and side-effects [24].

3.1.6. SWOG 9346

Patients received a 7-month induction treatment with LHRH agonist and an anti-androgen, following which they were randomized to CADT or IADT. Primary outcome measure was survival. Other outcome measure was QoL. A long-term follow-up for AEs was published recently [25].

3.2. Study outcomes

The key outcomes from the studies included in this review are summarized below and detailed in Table 4.

3.2.1. Median on- and off-treatment periods

In JPR.7, median on-treatment duration was nearly 2.9 times in CADT *vs.* IADT (43.9 months and 15.4 months, respectively). Median off-treatment period was 37.6 months, which was nearly 2.4 times of the on-treatment period [17]. In SEUG 9401, 50% patients were off-treatment for at least 52 weeks, and 29% were off-treatment for >36 months. Patients who achieved PSA <2 ng/mL, had a 74-week off-treatment period, and were on-treatment for 18% of their time in the study [20]. In SEUG 9901, 50% of the patients were off-treatment for at least 132 weeks, and 28% were off-treatment for >5 years. Median off-treatment period were 162 and 110 weeks for patients whose PSA levels were ≤1 and 1—4 ng/mL, respectively [21]. In TAP 22, the mean first off-treatment period was 126 days, which was 54.6% of the study treatment duration [22]. In Finn Prostate, median on-treatment period for first cycle was 24 weeks, while the median off-treatment period was 23.6 weeks, which gradually decreased with each subsequent cycle [23]. Median off-treatment period for first cycle in TULP was 13 months, which was 65% of their time in study [24]. The median on- and off-treatment periods were not evaluated in SWOG 9346 [25].

Table 4 Results of studies comparing intermittent androgen deprivation therapy (IADT) with continuous androgen deprivation therapy (CADT).

Study	Arms	Patients randomized, *n*	Off-treatment period	Progression, *n*	Time to progression	Inference (IADT *vs.* CADT)	Median follow-up time (year)	Total number of deaths, *n*	Overall survival, median	Prostate cancer deaths, *n*, median	Prostate cancer survival
SEUG 9401 [20]	IADT CADT	314 312	**Median** 52 weeks (50% patients); >36 months (29% patients)	127 107	HR (95%CI): 0.81 (0.63—1.05) for CADT *vs.* IADT; $p = 0.11$	No significant difference in survival outcomes. No overall HRQoL benefit except improved sexual activity in IADT group	4.25	170 169	HR (95%CI): 0.99 (0.80—1.23) for CADT *vs.* IADT; $p = 0.84$	74 65	HR (95%CI): 0.88 (0.63—1.23) for CADT *vs.* IADT. *p* value is not given in publication
TULP [24]	IADT CADT	97 96	**Mean** 1st cycle: 13 months (65% of cycle duration) 2nd cycle: 5 months (40% of cycle duration) 3rd cycle: 0.6 months (14% of cycle duration)	NA NA	NA NA	IADT is not a good option for patients with low PSA nadir	2.6	NA NA		NA	NA NA
Finn Prostate [23]	IADT CADT	274 280	**Median** 23.6 weeks (57% of cycle duration) in cycle 1 and 11.1 weeks (27% of cycle duration) in cycle 12	NA NA	34.5 months 30.2 months HR (95%CI): 1.08 (0.90—1.23) for CADT *vs.* IADT; $p = 0.43$)	No significant difference in survival outcomes	5.4	186 206	45.2 months 45.7 months; HR (95%CI): 1.15 (0.94—1.29) for CADT *vs.* IADT; $p = 0.17$	117 131	45.2 months 44.3 months; HR (95%CI): 1.17 (0.95—1.35) for CADT *vs.* IADT; $p = 0.29$
JPR.7 [17]	IADT CADT	690 696	**Median** 37.6 months (interquartile range 20.0—59.6 months)	202 patients HR (95%CI): 0.81 (0.68—0.98) for IADT *vs.* CADT; $p = 0.03$ 243 patients	NA	IADT non-inferior to CADT in survival outcomes. Some HRQoL factors improved	6.9	268 256	8.8 years 9.1 years; HR (95%CI): 1.02 (0.86—1.21) for IADT *vs.* CADT; $p = 0.009$	120 94	HR 1.23 (95%CI 0.94—1.66) IADT *vs.* CADT; $p = 0.13$
TAP 22 [22]	IADT CADT	86 83	**Mean** 126 days (54.6% of cycle duration) in cycle 1 and 85 days (42% of cycle duration) in cycle 7	NA NA	20.7 months (95% CI, 13.9—25.4 months) 15.1 months (95% CI, 12.1—22.7 months); ($p = 0.74$)	No significant difference in survival outcomes	3.7	49 45	42.2 months 52 months; $p = 0.75$	NA NA	NA NA

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Table 4 (*continued*)

Study	Arms	Patients randomized, *n*	Off-treatment period	Progression, *n*	Time to progression	Inference (IADT *vs.* CADT)	Median follow-up time (year)	Total number of deaths, *n*	Overall survival, median	Prostate cancer deaths, *n*, median	Prostate cancer survival
SEUG 9901 [21]	IADT 462 CADT 456		**Median** 162 weeks for PSA $\leq$1 ng/mL; 110 weeks for PSA 1-4	168 131; HR (95%CI): 1.16 (0.93–1.47) for IADT *vs.* CADT; $p = 0.195$	NA NA	No significant difference in survival outcomes. Improved HRQoL (sexual activity) in IADT group	5.5	258 267	HR (95%CI): 0.90 (0.76–1.07) for overall survival; $p = 0.252$	82 82	HR (95%CI): 0.93 (0.69–1.26) for overall survival; $p = 0.648$
SWOG 9346 [25]	IADT 770 CADT 765		>40% of time	NA	16.6 months 11.5 months; $p = 0.17$	IADT inferior to CADT. In patients with extensive disease, IADT is non-inferior to CADT. Small HRQoL improvements with IADT	9.8	483 445	5.1 years HR (95%CI): 1.10 (0.99–1.23) for overall survival in IADT group 5.8 years	386 325	NA NA

CI, confidence interval; HR, hazard ratio; HRQoL, health-related quality of life; NA, not available/applicable; PSA, prostate-specific antigen.

3.2.2. Post-treatment PSA levels—PSA progression/CRPC

In JPR.7, CRPC developed in a total of 445 patients (IADT = 202 patients, CADT = 243 patients). The estimated hazard ratio (HR) for time to CRPC was 0.80 (95% confidence intervals (CI): 0.67–0.98; $p = 0.02$) after adjustment for the stratification factors and 0.81 (95%CI 0.68–0.98; $p = 0.03$) after adjustment for potential prognostic factors. The authors noted that there could have been a possible delay in identifying patients with CRPC due to restart of the treatment in IADT group. Additionally, to be categorized as CRPC, these patients had to have a testosterone level below castrate levels and an additional three increases in PSA levels. This might have increased the apparent time to CRPC in IADT group, and possibly contributed towards longer overall survival in CADT group.

In SEUG 9401, there was a median 96% reduction from induction in PSA. Progression was reported in 234 patients (IADT – 127 patients, CADT – 107 patients). The estimated HR for time to any progression was 0.81 (95%CI 0.63–1.05; $p = 0.11$), which was slightly longer in the CADT group. In SEUG 9901, disease progression was reported in 299 patients (IADT 168 patients, CADT 131 patients). Progression-free survival was comparable between CADT and IADT groups (HR = 1.01; 95%CI: 0.86–1.19; $p = 0.89$). In patients with PSA $\leq$1 ng/mL, IADT was more effective than CADT (HR = 0.79; 95%CI: 0.61–1.02, $p = 0.07$).

In TAP 22, median overall progression-free survival was 20.7 months in IADT compared to 15.1 months in CADT ($p = 0.74$). There were 67 events of PSA progression in CADT and 70 in IADT group. In Finn Prostate, median time to progression was comparable in IADT and CADT groups (34.5 and 30.2 months, respectively; $p = 0.43$).

In TULP, the 2-year risk of PSA progression increased with higher PSA levels at baseline. The data showed the 2-year risk of PSA progression for baseline PSA <50 ng/mL, 50 –<500 ng/mL, and $\geq$500 ng/mL to be 25%, 55%, and 76% ($p = 0.03$) in CADT, and 38%, 64%, and 85% ($p = 0.006$) in IADT, respectively. Patients achieving PSA nadir of $\leq$0.2 ng/mL had significantly higher 2-year risk of progression compared to CADT group (53% *vs.* 31%; $p = 0.03$).

In Finn Prostate study, removing the patients with variable PSA in CADT and IADT groups from the analysis also showed similar results, though cancer-specific survival favored CADT. The QoL scores also remained comparable [35].

Post-treatment PSA levels or PSA progression was not evaluated in SWOG 9346.

3.2.3. OS

In JPR.7, IADT was non-inferior to CADT, with median OS being 8.8 and 9.1 years in the two groups, respectively (Table 4). Similar number of deaths was reported in both the groups. More prostate cancer deaths were reported in IADT group; however, this difference was not significant. The 7-year cumulative disease-related death rates were estimated at 18% and 15% for the IADT and CADT groups, respectively. It should be noted that for patients with non-metastatic disease, the planned follow-up for survival was probably shorter. Additionally, there was limited information about the numerically greater cause of deaths in CADT group, and also if these were due to treatment [17].

In SEUG studies, there were similar number of deaths in both the groups, and this trend was noted for prostate

cancer deaths as well. A subgroup of patients with PSA ≤1 ng/mL in SEUG 9901 showed better OS in IADT as compared with CADT group, although the difference was not statistically significance (HR = 0.79; 95%CI: 0.61−1.02, $p = 0.07$) [20,21].

In TAP 22, the median OS and deaths were comparable in CADT and IADT groups [22]. In Finn Prostate also, total number of deaths, deaths due to prostate cancer, and median time to death were comparable across groups [23].

Similarly, in SWOG 9346, deaths were comparable across the groups (445 *vs.* 483 in CADT *vs.* IADT, respectively). In the same study, median survival after randomization was slightly longer in CADT *vs.* IADT, translating into 10% relative increase in risk of death with IADT (HR = 1.10; 90%CI: 0.99−1.23). The upper limit of 90%CI was beyond the non-inferiority threshold of 1.20, which precluded a clear non-inferiority of IADT *vs.* CADT. Authors should also note that a claim for IADT's significant inferiority *vs.* CADT could not be made because the lower limit of the CI (0.99) did not exclude 1.00. These findings were supported by the secondary analysis [25].

3.2.4. Signs and symptoms, QoL

In JPR.7, for items pertaining to symptoms, IADT was associated with significantly better scores for hot flushes ($p < 0.001$), desire for sexual activity ($p < 0.001$), and urinary symptoms ($p = 0.006$), with a trend towards improvement in the level of fatigue ($p = 0.07$). The EORTC QoL-C30 showed subtle but non-significant scores in IADT compared to CADT [17].

In SEUG 9401, most of the domains of EORTC QoL-C30 did not show a difference between CADT and IADT, except for emotional domain and sexual functioning. Sexual activity decreased in both groups during the study; However, it was significantly better ($p < 0.01$) in the IADT group. After 15 months, more patients in IADT group reported sexual activity compared to CADT group (28% and 10%, respectively) [20]. In SEUG 9901, the same trend was observed. QLQ-30 scores gradually and similarly decreased in the two treatment groups, and were comparable between the groups. Though sexual activity decreased in both the treatment groups, it was significantly better in IADT group, and was restored as early as 6 months. This trend was also noted after 30 months of the treatment, with significantly higher proportion of patients reporting sexual activity in the IADT *vs.* CADT group (24.9% of 226 patients *vs.* 6.4% of 145 patients, respectively; $p < 0.0001$) [21].

In TAP 22, EORTC HRQoL showed no clinically relevant difference between CADT and IADT groups. Sexual functioning was significantly better in IADT group [22]. In Finn Prostate study, significant and favorable differences in EORTC HRQoL, with respect to activity limitation, physical capacity, and sexual functioning were noted in IADT compared to CADT group [23].

In TULP, no differences in EORTC QoL-C30 were observed in the two groups [24]. In SWOG 9346, patients in IADT group had fewer instances of impotence ($p < 0.001$), and had better mental health ($p = 0.003$) compared to CADT at 3 months. Libido scores were also numerically better in IADT group, though statistical significance as set at level 0.04 was not achieved. Following 9 months into the study, four of the five QoL outcome scores favored IADT over CADT; however, this benefit was sustained only for physical functioning at 15 months [25].

While considering the QoL data from these studies, one should bear in mind that the studies did not use exactly the same tools while assessing the impact on QoL, and hence may not be comparable to a full extent. Further, patients with greater disease burden tend to have a greater benefit in QoL compared to those with lesser disease burden, which may bias the true results.

3.2.5. AEs

Common AEs associated with ADT that largely influence the QoL includes hot flushes and sexual dysfunction. In JPR.7, IADT was significantly better than CADT with respect to hot flushes and sexual activity (both $p < 0.001$) [17]. In SEUG 9401, more AEs were noted in CADT compared to IADT group. Significantly higher proportion of patients in the CADT group reported symptoms of hot flushes, gynecomastia, and skin complaints (all $p < 0.05$). Importantly, the risk of cardiovascular disease-related deaths were greater in CADT compared to IADT group (16.7% *vs.*13.1%, respectively) [20]. In SEUG 9901, more AEs were reported in CADT with significantly greater incidences of hot flushes, gynecomastia, and headache as compared to IADT ($p < 0.001$) [21].

In TAP 22, treatment-emergent AEs (TEAEs) in CADT were significantly higher than in IADT (93.6% *vs.* 84.4%, respectively; $p = 0.042$). The most frequent AEs in CADT and IADT were hot flushes (63.8% and 60.4%), headache (46.8% and 32.3%), lumbar pain (13.8% and 12.5%), and joint pain (13.8% and NA), respectively. SAEs were reported in 29.8% patients in CADT and 31.3% patients in IADT. Most of the SAEs were unrelated to treatment (96%). Discontinuations due to AEs occurred in 9.6% and 7.3% patients in CADT and IADT groups, respectively [22].

In TULP, more AEs occurred in the CADT as compared to IADT group [24]. In SWOG 9346, the incidence of AEs, both cardiovascular and others, was comparable across the treatment groups. However, in a long-term follow-up, it was observed that incidence of AEs was similar across the two groups. Additionally, older patients in IADT group had a greater incidence of ischemic and thrombotic events as compared to younger patients [25]. Details of AEs experienced in some of the studies were given in Table 5.

3.2.6. Testosterone recovery

In general, the extent of testosterone recovery gradually reduced with each successive treatment cycle. This could be attributed to older age, low testosterone reserves, and time on-treatment. In TAP 22, testosterone levels were restored after 3 months of off-treatment period [22]. In Finn Prostate, mean and median plasma testosterone remained at a low level (<1.0 nmol/L) in the CADT group after randomization, but showed recovery at the end of each off-treatment period in the IADT group [23]. However, it did not reach the same level as at the end of the previous off-treatment period. In TULP, testosterone levels were restored eight months after the off-treatment period started; and 92% patients had normal testosterone levels by the end of first off-treatment period [24].

Table 5 Common adverse events in intermittent androgen deprivation therapy (IADT) and continuous androgen deprivation therapy (CADT) groups (% patients, ≥5% in any group).

Adverse events	SEUG 9401 [20]		TULP [24]		Finn Prostate [23][a]		TAP 22 [22]		SEUG 9901 [21]	
	IADT (n = 299)	CADT (n = 293)	IADT (n = 97)	CADT (n = 96)	IADT (n = 274)	CADT (n = 280)	IADT (n = 96)	CADT (n = 94)	IADT (n = 436)	CADT (n = 421)
Anemia			4	5						
Atrial fibrillation					5.5	5.7				
Bone pain							13.5	—		
Brain infarction					8.8	11.1				
Bronchitis										
Cardiac failure					7.7	6.4				
Constipation			7	17						
Coronary artery disease					7.7	10.7				
Diarrhea										
Depression			6	11						
Dyspnea			6	12						
Erectile dysfunction			9	10						
Gynecomastia	12.4	19.5	4	7					13.8	37.3
Headache	7.4	12.3					32.3	46.8	8.0	15.9
Hot flushes	19.7	30	50	59			60.4	63.8	8.3	24.9
Hypertension										
Increased liver enzyme			8	5						
Injection site reaction										
Joint pain							—	13.8		
Lumbar pain							12.5	13.8		
Myocardial infarction					6.9	7.9				
Nasopharyngitis										
Nausea			11	20						
Other	10.4	8.9							11.0	12.8
Other brain circulatory disorders					5.5	2.1				
Other singular vascular disorders					5.1	3.9				
Pruritus										
Skin complaints	2.7	6.8							0.7	1.7
Urinary incontinence										
Visual disturbances			33	33						
Weight gain										

[a] Cardiovascular adverse events only.

4. Discussion

The data from these seven studies indicates that IADT may be non-inferior, if not superior to CADT in patients with prostate cancer. However, any inferences drawn from this data should be taken with a pinch of salt for the following reasons. One has to understand that non-inferiority studies have unidirectional inference, and a lack of inferiority cannot always be interpreted as similarity. Besides this, disease burden, PSA cut-offs for patient eligibility, withdrawal and reinitiation of ADT, duration of induction treatment, agent used for ADT, age and prior experience with ADT may also govern the treatment outcome, and hence are key to have an optimum treatment outcome with IADT. Importantly, in patients given IADT, cardiovascular deaths may bias the results to a great extent, and it is important to adjust the survival data for cardiovascular disease-related deaths. Some of the crucial aspects while comprehending there data are discussed here.

One key challenge with study design preference is the definition of non-inferiority margin for comparing CADT and IADT. The assumptions in the three trials with non-inferiority design were:

- JPR.7 [17]: CADT, median survival 7 years, IADT was to be considered non-inferior if OS at 7 years was <8% points; upper limit of non-inferiority margin was 1.25;
- SEUG 9901 [21]: CADT, median survival 4.25 years, IADT was to be considered non-inferior if OS was shorter by 3.5 years than CADT, upper limit of non-inferiority margin was 1.21;
- SWOG 9346 [25]: CADT, median survival 35 months, IADT was to be considered non-inferior if overall survival was shorter by <7 months than CADT; upper limit of non-inferiority margin was 1.20.

These differences in non-inferiority margins have a significant impact on the outcomes [36]. Applying the non-inferiority margins from one study to another made a large difference to the results as shown in a recent review [37]. Therefore, a validated and stringently defined non-inferiority margin is highly warranted for studies comparing IADT and CADT.

Disease burden in prostate cancer is generally based upon the size of tumor, Gleason scores, metastatic status, spread to regional lymph nodes, and serum PSA. Of these factors, serum PSA and metastatic status have been key players in deciding the patient's eligibility criteria for IADT. Serum PSA is a surrogate marker of disease stage and activity, and its measurement is an innate part of the IADT for reinitiating treatment, and also for prognostic purposes [38]. The data show that PSA level <10 ng/mL at the start of treatment is associated with considerably longer remission than ≥10 ng/mL; PSA levels at treatment restart also have an impact on outcomes [39]. Therefore, it is important to have a practical and valid PSA cut-off for ADT restart as lower the PSA level, more likely is the earlier restart of ADT. Another important consideration is the metastatic status. Patients with locally advanced, metastatic prostate cancer may respond better to IADT than those with distant metastasis. Regarding metastatic status and spread to regional lymph nodes, it is believed that patients with non-metastatic disease, or patients with metastatic but locally advanced prostate cancer have a lower disease (tumor) burden.

Data from JPR.7 [17], SEUG [20,21], Finn Prostate [23], TULP [24] and SWOG 9346 [25] clearly indicate that patients with high Gleason score and metastases did not benefit much from IADT while patients with non-metastatic disease and local or biochemical failure after radiotherapy may benefit from IADT. Gleason score did not show any impact on treatment outcome in JPR.7.

In SEUG studies, both metastatic status and PSA levels were independently associated with OS and progression [20,21]. In SEUG 9401, for non-metastatic patients, HR for CADT *vs.* IADT was 0.86 (95%CI: 0.65–1.14), favoring CADT; while for M1 patients, the HR was 1.26 (95%CI: 0.90–1.78), favoring IADT. Additionally, deaths from any cancer were more common with IADT. The HR for disease-specific survival in the CADT (65 deaths) *vs.* IADT (74 deaths) was 0.88 (95%CI: 0.63–1.23). More deaths occurred from second primaries in IADT group thereby favoring CADT (HR = 0.59; 95%CI: 0.34–1.05).

In Finn Prostate, which included M1 patients (a group with a higher disease burden), there were no notable differences between the two groups [23]. However, in SWOG 9346, PSA level of ≤4 ng/mL after 7-month ADT, emerged as a strong predictor of survival in patients with metastatic cancer ($p < 0.001$), especially patients who achieved PSA levels <0.2 ng/mL [25]. This is supported by the finding from an analysis of two studies where PSA nadir and PSA >5 ng/mL were associated with an increased risk of prostate cancer-specific mortality [40]. Therefore, achieving PSA nadir of <0.2 ng/mL or lower may indicate a longer off-treatment period and hence a better treatment outcome with IADT.

Another important finding was the emergence of PSA criteria to identify CRPC as a confounding factor in JPR.7 [17]. To identify CRPC in JPR.7, patients had to have three consecutive increases in PSA along with castrate levels of testosterone. However, this inadvertently increased the time to CRPC in IADT group, possibly delaying the identification of patients with CRPC. These findings are important because patients with higher baseline PSA, those failing to achieve PSA <4 ng/mL with induction therapy, and those with distant metastases will probably have an earlier restart of ADT and hence a shorter off-treatment period, which will probably be as good as CADT regimen. Having said this, one should be careful while offering IADT to patients with high disease burden.

Testosterone recovery is one of the key benefits of IADT and often most valued by the patients. However, the extent of recovery goes down with each successive cycle [30]. Monitoring testosterone levels is important to have an adequate cancer control, mainly due to two contrasting reasons. To delay the disease progression, it is important to maintain castrate levels of testosterone as these may accelerate PSA doubling time. On the other hand, prolonged testosterone suppression may increase the risk to cardiovascular disease and osteoporosis [41]. In JPR.7, only 35% of patients had testosterone recovered to pre-treatment levels within 2 years after completing the first period of treatment, and 79% of patients had a level as per

eligibility criteria (144 ng/dL) [17]. The data also showed that patients >75 years of age were less likely to return to pre-treatment testosterone levels *vs.* younger counterparts ($p = 0.001$). Of the men who were potent at baseline, only 29% could recover their potency.

The availability of an off-treatment period, the biggest selling point of IADT, is particularly important as it provides a relief from treatment-related AEs, and a period where possibly testosterone recovery occurs. The trend across the published studies is similar; off-treatment period generally decreases with subsequent cycles [42]. The off-treatment period ranged from less than 6 weeks to >87 months after first cycle in published studies [43,44]. The median off-treatment period was 15.4 months in a meta-analysis of 10 trials [39]. This clearly suggests that there is a high variability in this regards. Considering the fact that off-treatment period is the most sought-after benefit of IADT, it is important to focus on the duration of off-treatment period during first as well as successive cycles. Furthermore, a practical approach could be if PSA cut-off levels to enter the off-treatment period should change for subsequent cycles.

Testosterone recovery and reduced AEs during the off-treatment period directly contribute to an improved QoL. In almost all the studies, there was a subtle improvement in QoL, though a clear significance in this regard is seldom achieved. Klotz [45] discussed the reasons for this subtle and non-significant improvement in QoL. Notable points were measuring QoL benefit before testosterone restoration, domains evaluated, and the tool used for measuring QoL. QoL is largely influenced by the duration of off-treatment period, testosterone recovery and potency, and the overall importance of the same for the patient. Similar inference was discussed in JPR.7 [17], suggesting that some patients in IADT group may restart therapy based on rising PSA levels, and therefore, the actual effect of the off-treatment period on QoL due to lack of testosterone restoration could remain feeble. Nonetheless, it should be noted that patient preference and patient's perspective on HR QoL are of utmost importance, and even partial non-significant relief in overall QoL with a high clinically meaningful impact on sexual functioning may mean a large benefit to many patients.

In summary, it is still difficult to clearly segregate the patients who would or would not benefit from IADT because most of the trials included mixed patient populations, i.e. patients with metastatic and locally advanced cancer. Importantly, many of these patients do not achieve PSA levels which could have led them to have an off-treatment period, which means a smaller than required sample size, and hence lack of true significance, if any. Other operational level challenges with these studies were lack of consistency in study designs, non-inferiority margins for non-inferiority studies, on- and off-treatment criteria, PSA and/or testosterone eligibility criteria, type of hormonal therapy, and variability amongst outcome measures across trials, which seem to play an important role in the inadequacy of data supporting IADT. Non-inferiority margins remain an important point of discussion as far as study outcomes in terms of OS and progression-free survival are concerned. Other characteristics may also have significantly impacted the findings in these studies such as tumor grade, comorbidities, PSA doubling time, and life expectancy.

Cumulative data suggest that younger patients, those with lower disease burden (moderately elevated PSA, low tumor burden, preferably non-metastatic), and those who highly weigh sexual functioning should be the key factors while considering IADT. The data from SEUG studies [20,21] showed that patients aged <75 years, PSA <2 ng/mL, and a Gleason score of <7 had a better prognosis as noted by a slower disease progression and a better QoL. This also means that patients with high tumor burden (high Gleason score, metastasis, PSA >100 ng/mL, PSA doubling time >5 ng/mL/month), those not achieving PSA nadir of <4 ng/mL after 6-month induction, and those with PSA doubling time >5 ng/mL/month may not be good candidates for IADT [18,46].

It has been recommended that the induction period should be between 3 and 9 months since it may take up to 9months for optimum PSA suppression (Table 4). Once PSA is < 4 ng/mL for metastatic disease, or <0.5 ng/mL for recurrent disease, patients can enter the off-treatment period. ADT can be restarted when PSA reaches 4—10 ng/mL in non-metastatic cancer, or 10—15 ng/mL in metastatic cancer. Patients should be closely followed-up for disease progression and PSA and testosterone levels every 3—6 months. However, if the patient fails to achieve PSA <0.2—0.4 ng/mL, they should continue the ADT (CADT). Successive cycles may have a minimum of 6-month induction.

5. Conclusion

IADT seems to be as efficacious as CADT, especially in patients with lower disease burden; however, one should also remember that careful patient selection is the key to a good outcome. This implies that patients who achieve PSA <4 ng/mL during the 5—7-month induction period, have poor tolerability to CADT, have non-metastatic disease, or metastasis limited to lymph nodes, have locally advanced disease, are older, have Gleason scores >7, and have longer PSA doubling time may actually benefit with IADT. Importantly, this is the population that may truly benefit in terms of improved OS, slower time to progression, and have an improved QoL. Therefore, to achieve the maximum treatment benefit, it is important to closely monitor the patients on IADT for PSA and testosterone levels.

Conflicts of interest

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