# Revisiting Intermittent Therapy in Metastatic Prostate Cancer

## Can Less be More in the *"New World Order?"*

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**Abstract**

**Context:** Androgen deprivation therapy (ADT) is the standard-of-care for men with metastatic hormone-sensitive prostate cancer (HSPC) and a potential treatment option in those with PSA relapse post local therapy. Based on promising biological and preclinical data several clinical trials compared the efficacy of intermittent (IAD) vs. continuous (CAD) with the objective of delaying disease progression and improving quality of life.

**Objective:** The objective of this review is to revisit the concept of IAD in the "new world order" and reconsider if it has a potential clinical role in an era where we have seen unprecedented progress in the management of patients with metastatic HSPC.

**Evidence Acquisition:** MEDLINE, Embase and the Cochrane Database were searched for randomized, controlled trials comparing IAD and CAD therapy. References of retrieved articles were also searched. Articles with at least 100 randomized patients that were published in 2008 or later and had data on overall survival or quality of life (QoL) outcomes were included.

**Evidence Synthesis:** The evidence to date cannot exclude inferiority of IAD compared to CAD with respect to survival outcomes. The hazard ratios in metastatic disease indicate less favorable survival with IAD. No superiority trial conclusively favored IAD or CAD. Two trials demonstrated non-inferiority of IAD; though the non-inferiority margins are clinically concerning. Another trial could not exclude non-inferiority. A modest but temporary QoL and symptom benefit generally favoring IAD was observed.

**Conclusions:** IAD has not conclusively demonstrated an impact on disease progression or survival and has only modest effects on QoL and symptoms measured in the short-term. As such, it is not standard-of-care, particularly in the era where we have seen unprecedented survival

impact with combination ADT + docetaxel or abiraterone +prednisone. IAD may need to be reassessed in the context of current therapies, ideally driven by biological rationale, with the goal of minimizing physical and financial toxicities with appropriately designed informative clinical trials.

**Patient Summary:** In this report we looked at two hormone therapy approaches for prostate cancer that is still sensitive to castration: one with treatment breaks and one without. Patients may tolerate therapy with breaks more easily but this effect is not sustained and is not associated with better longevity. The best longevity is seen in patients who receive newer hormone therapies or chemotherapy in addition to continuous hormone therapy. Whether these newer therapies would be as effective if given intermittently is an important but unanswered question.

## Introduction

Ever since 1941, when Huggins and Hodges demonstrated that prostate cancer (PC) is an androgen driven disease and that androgen deprivation therapy (ADT) via surgical or medical castration can induce significant regressions of PC,[1] ADT has been the standard-of-care for patients with newly diagnosed metastatic disease. Despite high and potentially durable response rates, the majority of patients will develop disease progression. Progression to castration resistance (CRPC) is likely a function of clonal selection and adaptation via androgen signaling dependent and independent mechanisms. CRPC is lethal in virtually all patients with a median overall survival (OS) of 35 months with current therapies.[2-4]

Over the past seven decades, various strategies were tested to enhance efficacy and/or minimize castration related side-effects. These strategies included medical castration (estrogen, or LHRH targeted therapy), peripheral blockade, combined androgen deprivation, ADT +/- bone targeted therapy, intermittent ADT (IAD) and most recently ADT + docetaxel or abiraterone/prednisone.

Considering the burdens of ADT,[5] IAD was an attractive option conceptualized in the late 1980s. IAD is one of the most tested treatment strategies in different PC disease settings in the past 20+ years. Its attractiveness was based on the premise of minimizing ADT related side-effects while maintaining or potentially improving the anticancer effect based on pre-clinical data. IAD has not lived up to the expectations as it has not resulted in demonstrable benefits in DFS (disease-free survival) or OS. The unprecedented impact on survival in patients with metastatic PC with the use of docetaxel or abiraterone/prednisone in combination with continuous ADT (CAD) raises the question if IAD has any role in the "New World Order," and if so, why and how.

In this overview we will discuss the history of IAD, the evidence from randomized clinical trials comparing IAD to CAD and discuss the potential future of “intermittent therapy” in this new era of advanced PC therapies.

**Intermittent ADT: History and biologic rationale**

The biologic rationale for IAD was based on PC heterogeneity; tumors are composed of androgen-dependent and independent cells, and relapse while on AD was due to clonal expansion of androgen-independent cells. Several pre-clinical studies supported this hypothesis. In 1979, researchers demonstrated that when the androgen-dependent Shionogi medullary carcinoma 115 (SC115) was transplanted into castrated male mice or female mice, androgen-independent spindle cell tumors grew, becoming the dominant cell type.[6] This suggested a cellular heterogeneity of the original tumors composed of both androgen-dependent and androgen-independent cells. The rat prostate adenocarcinoma R-3327 demonstrated similar heterogeneity.[7] Bruchovsky et al. demonstrated that in androgen-sensitive Shionogi mammary carcinoma, castration increased the proportion of androgen-independent tumor stem cells.[8] Shortly thereafter, preclinical studies in murine models demonstrated a plausible biologic mechanism for delayed castration resistance with IAD. Akakura et al. and Sato et al. demonstrated that xenograft prostate tumors responded to multiple cycles of ADT in mice with significant prolongation of time to CRPC.[9,10]

Combined, these data suggested that androgen-sensitive tumors survived castration through androgen-independent stem cells within the tumor. The selective pressure in an androgen-depleted milieu allows them to become the dominant cell type within the tumor. Re-exposure to androgens allows the androgen-dependent stem cells to regrow and sensitizes the tumors to further castration. One important factor to consider in the aforementioned translational studies is that in the experimental models used (transplanting tumor after castration in intact mice), the levels of testosterone "recovered" immediately; tumors were exposed to either castrate or physiologic levels of testosterone. Following this work, several clinical trials using IAD

suggested this approach was feasible and allowed for recovery from the short-term, reversible adverse effects of ADT, leading to randomized phase III trials.[11-13]

The rationale for implementing IAD in patients—in addition to prolonging time to CRPC—was based on the goal of minimizing therapy related toxicity. Diethylstilbestrol (DES) was the standard pharmacologic method of castration until luteinizing hormone releasing hormone (LHRH) agonists were developed, and they carry toxicities including cardiovascular, thromboembolic, neurologic and psychiatric toxicity,[14-17]hence, the drive to improve the therapeutic index of PC treatment with IAD.

**Evidence acquisition**

We searched Medline (via PubMed), Embase and the Cochrane Library databases for articles comparing IAD with CAD that were published in the last 10 years. Search terms used for each database can be found in the supplementary appendix (page 2). Validated filters were used to narrow searches to randomized control trials (RCTs).[18,19] References of any articles included in the review and any meta-analyses found were searched for additional relevant articles. Only RCTs with data on survival or HRQoL and ≥100 patients randomized were included. 21 full-text articles were initially included, and 10 were included in final analysis. The preferred reporting item for systematic reviews and meta-analysis (PRISMA) diagram is shown in the Supplementary Appendix (**Figure S1**).[20] Clinical trials databases, including clinicaltrials.gov, WHO ICRTP and ISRCTN.com, were searched for ongoing trials. Level of evidence (LOE) and recommendations were based on Oxford Center for Evidence-Based Medicine.[21]

## Evidence Synthesis

*Deconstructing the Evidence: Survival Outcomes*

Nine phase III randomized controlled trials comparing IAD and CAD with mature data on survival were included (**Table 1**).[22-30] The trials were heterogeneous with respect to trial's design (non-inferiority vs. superiority), the size of the respective non-inferiority/superiority margins, patient population (M0 or M1 only vs. M0 and M1), treatment discontinuation re-initiation thresholds (**Table 2**) and primary outcome measure (progression-free survival vs. OS). Two studies randomized all patients starting ADT;[22,24] the others selected for patients who had already responded to induction ADT for randomization. In Irani et al.,[22] all patients proceeded to randomized treatment allocation. In PR.7,[24] 1364 of 1386 randomized patients received their assigned therapy. Time spent off ADT varied between the trials based on study design and thresholds for retreatment.

None of the reported superiority studies demonstrated a survival benefit in favor of IAD (LOE: 1b).[22,23,25,26,29,30] Of the non-inferiority studies, SEUG 9901 (LOE: 1b) and PR.7 (LOE: 1b) demonstrated non-inferiority of IAD compared with CAD with respect to their primary endpoints of survival.[24,28] One must keep in mind the generalizability of these studies since a majority (89%) of patients in SEUG 9901, and all patients included in PR.7 had M0 disease. There were notable competing risks: only 164/525 (31%) deaths in SEUG 9901 and 214/524 (41%) deaths in PR.7 were attributed to PC. In a post-hoc analysis, the PR.7 authors found that there was a trend towards worse PC-specific mortality (HR 1.18 95% CI: 0.90 – 1.55) in the IAD arm. Given that PR.7 and SEUG 9901 were largely conducted in M0 patients, long-term follow-up is needed to assess if there are any differences in survival, supplemented with

consistently collected quality of life (QoL) data throughout the later time points. While the authors concluded that the study demonstrated non-inferiority, of concern is the non-inferiority margins (NIMs) chosen: 1.25 in PR.7, and 1.21 in SEUG 9901. The observed median survival in the two trials' control arms were greater than expected—9.1 vs. 7 years in PR.7 and 5.8 vs. 4.25 years in SEUG 9901. Given the lower than expected event rate, the NIMs of the two trials implied that differences as great as 21.8 months and 12 months, respectively, in survival would be considered "noninferior," which is an important limitation in the design of these trials. While the observed HRs were close to 1, these limitations are important to understand in order to learn from potential pitfalls while designing future trials in the new age of PC therapy.

In a study of M1 patients, SWOG 9346 did not demonstrate non-inferiority of IAD with respect to survival (LOE: 1b).[27] The median survival was: CAD 5.8 years vs IAD 5.1 years with a HR of 1.10 with a 95% confidence interval (0.99 – 1.23) extending beyond the study's pre-specified NIM of 1.20. SWOG 9346 had substantially longer follow-up (9.8 years) in patients who had lower expected survival compared with PR.7 and SEUG 9901, and most deaths in SWOG 9346 were from PC (73% in CAD arm and 80% in IAD arm), supporting the internal validity of this study. The median OS observed was 5.8 months in the CAD arm compared to 5.1 months in the IAD arm; the HR upper limit of 1.23 would be consistent with an absolute survival difference of around one year in favor of CAD. While the trial was not powered to prove superiority of CAD compared to IAD at this magnitude, the point estimate of the survival difference seen is clinically meaningful and argues for CAD as standard of care in these patients.

Though authors have attempted to combine the results from these and other trials, one should interpret these results with caution due to the heterogeneity described above and the high risk of bias (including bias due to competing risks of endpoint) in the incorporated studies.[31]

*Quality of Life, Symptom Burden, Adverse Effects and Cost*

While survival is the outcome by which therapy impact is typically measured, the impact on QOL and adverse effects are very relevant clinical measures of disease control and treatment effects. Ten trials assessed whether or not IAD led to changes in HRQoL and self-reported symptoms when compared with CAD (**Table 3**; LOE: each 1b).[22-30,32,33] Using questionnaires, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and a PC specific module (EORTC QLQ-PR12 or 25), investigators attempted to quantify the HRQoL benefit inherent in IAD. In several trials, various domains—usually related to physical or sexual functioning—within the questionnaire favored those in the intermittent arm with statistical significance,[26,27,29] but the differences were either short-lived, clinically insignificant, or their magnitude lacked consistency across studies.

Irani et al. demonstrated that patients receiving IAD had improved erectile function (p=0.007), but had greater need for painkillers (p=0.02).[22] In SEUG 9401, QOL scores were improved in the continuous arm with respect to emotional domain (3.0 points better; p=0.01), severity of nausea and vomiting (p=0.01) and severity of insomnia (p=0.03).[23] Additionally, the global QoL scores in the QLQ C30 and overall QoL in the EORTC PC module were 2.7 and 3.0 percentage points better in the CAD group (p=0.05 and 0.04, respectively), though the authors note that the magnitude of difference was clinically insignificant. The investigators of TAP22 concluded that there were no clinically meaningful differences in QoL scores, and no trends could be observed.[25] In FINN-PROSTATE VII, activity limitation, physical capacity and sexual function scores significantly favored IAD in six, eight and eight of 20 treatment periods, respectively, while sexuality favored the CAD arm in eight of 20 treatment periods (each treatment period defined as the average length of time in intermittent arm receiving ADT or off-treatment).[33] In

SWOG 9346, patients on IAD reported impotence less frequently than those receiving CAD and had significantly better mental health ($p<0.001$ and $p=0.003$, respectively) at three months after randomization but not therafter.[27] This is not consistent with the expected testicular recovery. At other pre-specified time points there were no statistically significant QoL differences observed. In a study of Medicare claims of patients in who participated in SWOG 9346, ten-year cumulative incidence of ischemic and thrombotic events (myocardial infarction, severe thrombosis and ischemic heart disease) was 33% with IAD, compared with 24% in the CAD arm.[34]. Other reported adverse events were similar between the two groups. SEUG 9901 demonstrated improved symptom burden ($p=0.0001$) and sexual activity ($p<0.0001$) and fewer sexual problems ($p=0.0001$) in the IAD arm.[28] Verhagen et al. demonstrated limited improvement in QoL scores for patients receiving IAD in physical (88 vs 87.1 out of 100; $p=0.003$) and emotional functioning (92.5 vs 91.5 out of 100; $p<0.001$).[29] QoL scores in cognitive functioning were better in the group receiving CAD (88.4 vs 83.4; $p<0.001$). For studies utilizing the EORTC QLQ-C30, score differences of ~2.5 to 10 correlate with "little" change on the subjective symptom questionnaire, though others argue that absolute changes of 10 on the 100-point scale are better indicators of whether patients require supportive care changes.[35-37] IAD showed benefit with respect to patient symptoms, particularly hot flashes,[23,24,28,29] though Salonen et al. reported an increase in erectile dysfunction and depression in the IAD arm (**Table 3**).[33]

Although there is little reported comparative cost-effectiveness data for these regimens, the cost of ADT before disease progression is potentially lower with IAD compared to CAD in drug form, but not compared to bilateral orchiectomy. Verhagen et al. included financial worry in their study as a patient-reported outcome, which favored the IAD arm.[29] A systematic review of

trials comparing IAD with CAD estimated that IAD decreased the cost per patient per year in the USA by 48% from CAD; $5,000 vs $15,000 per year in the continuous arms (LOE: 4).[38] The cost savings were likely an underestimate, given their basis on total drug costs, and the authors were unable to include costs for treatment and hospitalizations related to adverse effects of treatment; some of the cost savings might be offset by closer follow-up and more intensive active surveillance in men receiving intermittent therapy.

## Discussion

No major randomized trials comparing CAD with IAD are yet to report. As previously constructed, the paradigm for IAD has "not lived up to expectations," despite the conclusions of PR.7 and SEUG 9901.[24,28] Evidence from SEUG 9901 and PR.7 suggesting that IAD is "equivalent" to CAD in M0 disease should be interpreted with caution. Assessing the effect of interventions on OS in non-metastatic PC is difficult due to competing causes of death in an elderly male population, and metastasis-free survival (MFS) is a validated surrogate endpoint for OS in localized PC. PR.7 did not assess metastasis-free survival, though while it "demonstrated equivalent OS," PC-specific mortality trended in favor of CAD group. In SEUG 9901, PFS trended towards improved outcomes in the CAD group as well. Combined with SWOG 9346, these non-inferiority trials have demonstrated that CAD is associated with better oncologic outcomes.

### *Testosterone Kinetics in Clinical Trials*

The kinetics of testosterone recovery in the clinical trials did not emulate the pre-clinical models by Akakura and Sato, when tumors were exposed to binary levels of testosterone – castrate and physiologic.[9,10] For example, Langenhuijsen et al. reported that for the first off-treatment period,

which lasted an average of 13 months, the average duration of castrate levels of testosterone in patients was 7 months. Patients were castrate for nearly the entirety of second and third off-treatment periods.[32] Other studies showed similar testosterone kinetics and recovery during off-treatment cycles.[24,26] Several phase II studies have also analyzed testosterone kinetics and recovery. Bruchovsky et al. demonstrated that 75% of men achieved testosterone recovery to low-normal range (2.5 ng/mL) during their first off-treatment period, with declining numbers in subsequent cycles.[39] Tunn et al. demonstrated a median testosterone recovery to low-normal range (2.3 ng/mL) of 100 days in the first off-treatment period and 115 days in the second round.[40] Ng et al. found that median recovery to eugonadal levels of testosterone (10.0 ng/mL) was 10.4 months.[41] Crook et al. demonstrated that 73% of patients recovered to normal testosterone levels, but their off-treatment times were subsequently shorter.[42] Therefore, many men who resume IAD due to rising PSA during a break from hormone therapy do not experience the immediate re-sensitization to testosterone that formed the biologic basis for IAD, nor will they experience significant HRQoL benefits, since HRQoL recovery in IAD is associated with testosterone recovery.[43] This aspect of testosterone recovery may explain the surprisingly modest, short and inconsistent effect of IAD on HRQoL and long-term adverse effects observed in the above trials.

One alternative strategy that more closely resembles the original biologic rationale of IAD is bipolar androgen therapy (BAT), by which patients would receive periods of ADT alternated with supraphysiologic doses of testosterone. Initial pre-clinical and clinical studies show promise,[44,45] but BAT needs more rigorous study specifically in patients with hormone-sensitive PC (HSPC) prior to large-scale clinical trials.

***The New Standard-of-care Is No Longer CAD Only***

Current systemic therapy for metastatic HSPC has itself changed; the standard-of-care tested in those older trials is no longer standard-of-care today. Recent studies have shown the unprecedented survival benefit of adding docetaxel or abiraterone acetate (AA) to CAD in metastatic HSPC (mHSPC).[46-49]

Adding to the results of CHAARTED, GETUG-AFU-15, STAMPEDE and LATITUDE,[46,47,50] will be PEACE-1. This is a 2 x 2 factorial trial examining the efficacy of combining docetaxel with AA and ADT in mHSPC (ClinicalTrials.gov identifier NCT01957436). Three other phase III studies are evaluating the second-generation AR antagonists apalutamide, darolutamide and enzalutamide in mHSPC (NCT02489318, NCT02799602 and NCT02446405). Patients in the darolutamide trial received concomitant ADT and docetaxel with or without darolutamide.In the other two trials, patients will receive concomitant ADT and they both stratify for use of docetaxel. The multi-arm STAMPEDE trial will combine enzalutamide with AA in upcoming years. The data from these trials will be important in ushering in an era of multimodal therapy.

However, as multimodality therapy including LHRH agonists, novel anti-androgens, biosynthesis inhibitors, chemotherapy and their combination are used earlier in PC, old challenges will resurface. As PC patients live longer, treatment-related adverse effects and cost will be more prominent. AA and enzalutamide can increase the risk for cardiovascular disease and hypertension,[51] and as these therapies are used earlier in PC, regimens limiting the overall exposure of patients to these drugs will be important in mitigating cardiovascular and other toxicities. As before, when IAD was first conceived as a method for improving QoL in patients

with PC, we must strive to find a method of therapy "de-intensification" that preserves efficacy and disease control while providing relief from physical and monetary costs.

***Intermittent therapy in the New World Order: Potential Strategies and Pitfalls***

One possible method of intermittent therapy might consist of an induction-consolidation model with the hope of inducing prolonged remission in patients with PC via a maximal cytotoxic anti-tumor strategy upfront, followed by a period of observation or less intensive therapy. As the initial pre-clinical studies demonstrated, PC is a heterogeneous disease with androgen dependent and independent cell populations. A multimodal strategy upfront may induce prolonged remission, with agents such as docetaxel + AR targeted and other targeted agents in appropriately selected patients working to kill tumor cell populations with *de novo* androgen independence.[52] An induction phase could consist of six cycles of docetaxel, CAD and a novel anti-androgen or biosynthesis inhibitor (or both), resembling the therapy currently undergoing investigation in the PEACE-1 (NCT01957436) and ARASENS (NCT02799602) trials. A consolidation phase after the administration of docetaxel would follow, consisting of ADT with oral anti-androgens or biosynthesis inhibitors and other targeted agents for a finite duration of time.

There are potential pitfalls with this strategy with respect to clinical trial design. Not every patient will be a suitable candidate; appropriate patient selection will be paramount, and trial designs to ensure true non-inferiority with clinically acceptable margins is very critical.

IAD is no longer the most critical question in an era where we have seen real progress emerging from maximizing AR targeting and multi-targeted approaches. Metastatic PC continues to be deadly; we therefore need to maximize the anticancer treatment effect with the hope for "cure"

or meaningful disease control and potential for long treatment holidays. Consideration for treatment holidays can be evaluated in patients with a better prognosis, regardless of the treatment schedule and design. Based on SWOG 9346 and CHAARTED, PSA response may be a plausible method of patient selection, since patients achieving a PSA nadir $\leq$0.2ng/mL is associated with better survival, even in patients with high-volume disease.[53,54]

This limited pool of patients combined with the increased survival seen in metastatic CRPC, will make trial design, accrual and completion more challenging, as prolonged follow-up time with thousands of patients will be required to exclude clinically meaningful differences in survival via non-inferiority trials. While MFS has emerged as an important intermediate clinical endpoint for survival in PC, similar validated intermediate clinical endpoints are lacking in patients with mHSPC.[55,56] Therefore, one must consider the opportunity cost of designing trials aimed at de-intensification of therapy via the intermittent approach, as they would need to be large-scale endeavors with significant follow-up that would compete with concurrent phase III trials aimed at increasing survival (**Table 4**). In an era when advances for HSPC are being achieved and there are still survival advantages to be gained, we should consider the following: when in the future is it worth devoting the resources to a method of de-intensification?

Certainly, on an individual patient basis IAD can be considered based on shared and informed decision. Though there is moderate evidence for improved tolerability in randomized trials (LOE: 2b), experienced clinicians recognize the benefits for patients they treat with IAD.[57] But the decision to use IAD must be made with both the clinician's and patient's mutual understanding that the patient's survival may be negatively impacted, especially without data on intermittent therapy in the state of PC care as it is today.

## Conclusions

In a deadly stage of disease for the majority of patients, the priority should be focused on maximizing the clinical benefits while minimizing treatment adverse effects. In this context the potential for de-intensification of therapy is critical. However, we must learn from prior experience and the lessons provided by the previous trials comparing IAD and CAD.

As noted in a prior review on IAD and CAD,[58] the NIMs used in the trials would have resulted in unacceptable outcomes. Certainly "One Size Does Not Fit All," thus future trials testing de-intensification strategies should carefully select appropriate patient subgroups, particularly after therapy efficacy outcomes have been optimized. Patient preferences regarding the potential losses in disease control they would be willing to trade off for possible benefit in QoL should be explored, as has been done in other solid tumors.[59]

| Trial/Author | Paper Year | N | ADT | Population | | Design | Median FU (y) | HR | CI |
|---|---|---|---|---|---|---|---|---|---|
| | | | | M0 | M1 | | | | |
| Irani et al.[22] | 2008 | 129 | Starting | M0 | M1 | Sup | 3.7 | 1.67[γ] | 0.77–3.33 |
| SEUG 9401[23] | 2009 | 626 | Responding | M0 | M1 | Sup | 4.3 | 0.99 | 0.80–1.23 |
| PR.7[24] | 2012 | 690 | Starting | M0 | --- | Non-inf NIM 1.25 | 6.9 | 1.02 | 0.86–1.21 |
| TAP22[25] | 2012 | 173 | Responding | --- | M1 | Sup | 3.7 | NK[ϕ] | NK |
| FINN PROSTATE VII[26] | 2012 | 554 | Responding | M0 | M1 | Sup | 5.4 | 0.87[γ] | 0.71–1.06 |
| SWOG 9346[27] | 2013 | 1535 | Responding | --- | M1 | Non-inf NIM 1.20 | 9.8 | 1.10 | 0.99–1.23 |
| SEUG 9901[28] | 2014 | 918 | Responding | M0 | M1 | Non-inf NIM 1.21 | 5.5 | 0.90 | 0.76–1.07 |
| Verhagen et al.[29] | 2014 | 258 | Responding | --- | M1 | Sup | 3.3 (mean) | NK[ϕ] | NK |
| ICELAND[30] | 2016 | 701 | Responding | M0 | --- | Sup | NR | NK[ϕ] | NK |

**Table 1. Overall Survival in randomized trials of IAD vs. CAD.**

Hazard ratios (HR) and confidence intervals (CI) reported with CAD as reference treatment unless otherwise noted. Non-inferiority margins (NIM) provided in non-inferiority trials.

[γ]HR estimates have been inverted so that the reference group is the continuous arm for each trial.[22, 26]

[ϕ]NK: Outcome not known but reported as "not statistically significant"

**FU=follow-up**

| Trial or Author | ADT Discontinuation Threshold | ADT Resumption Threshold |
|---|---|---|
| Irani et al.[22] | 6 months | 6 months |
| SEUG 9401[23] | 1. PSA < 4ng/mL or<br>2. PSA decrease by 80% | 1. PSA of 10ng/mL in symptomatic patients or PSA of 20ng/mL in asymptomatic patients<br>2. PSA rise of ≥ 20% from nadir |
| PR.7[24] | 8 months if PSA < 4ng/mL and no more than 1ng/mL above previous value in the treatment cycle | PSA of 10ng/mL or clinical evidence of disease progression |
| TAP22[25] | PSA < 4ng/mL | PSA of 10ng/mL or clinical evidence of disease progression |
| FINN PROSTATE VII[26, 33] | PSA < 10ng/mL | PSA of 20ng/mL or above the baseline PSA value after 24 weeks |
| SWOG 9346[27] | PSA < 4ng/mL after 7 months of treatment | PSA of 20ng/mL or above the baseline PSA value; at the investigator's discretion, PSA of 10ng/mL or symptoms |
| TULP[32] | PSA < 4ng/mL | M0 patients: PSA rise ≥ 10ng/mL<br>M1 patients: PSA rise ≥ 20ng/mL |
| SEUG 9901[28] | PSA <4ng/mL | PSA of 20ng/mL or symptoms due to disease |
| Verhagen et al.[29] | 1.PSA < 4ng/mL or<br>2. PSA decrease by 90% | 1. Clinical progression<br>2. PSA ≥ 200% of nadir value and PSA ≥ 50ng/mL<br>3. PSA ≥ 1,000ng/mL |
| ICELAND[30] | PSA ≤ 1ng/mL | PSA ≥ 2.5ng/mL |

**Table 2. Treatment discontinuation and re-initiation thresholds in intermittent therapy arms of included trials.**

Abbreviations: PSA=prostate-specific antigen; M0=non-metatastatic disease; M1=metastatic disease

| | | Patient-reported | | | | Clinician-collected | | |
|---|---|---|---|---|---|---|---|---|
| **Trial or Author** | **Year** | **QOL measurement** | **QOL domain favors IAD** | **--** | **QOL domain favors CAD** | **AE favors IAD** | **--** | **AE favors CAD** |
| Irani et al.[22] | 2008 | 1. QLQ-C30<br>2. EORTC PC module | Erectile function | -- | Need for painkillers | None | -- | None |
| SEUG 9401[23] | 2009 | 1. QLQ-C30<br>2. EORTC PC module | None | -- | Nausea and vomiting, Insomnia, Emotional domain | Hot flushes<br>Gynecomastia<br>Skin complaints | -- | None |
| PR.7[24] | 2012 | None | N/A | -- | N/A | Hot flashes<br>Sexual desire<br>Urinary symptoms | -- | None |
| TAP22[25] | 2012 | QLQ-C30 | None | -- | None | Total AE<br>Hot flushes<br>Headaches | -- | None |
| FINN PROSTATE VII[26, 33] | 2012 | Unspecified PC module | Activity limitation<br>Physical capacity<br>Sexual function | -- | Sexuality | None | -- | Erectile function<br>Depression |
| SWOG 9346[27] | 2013 | SWOG QOL q'aire | Impotence and Mental health (at 3 months only) | -- | None | None | -- | Thrombo-embolic events |
| TULP[32] | 2013 | 1. QLQ-C30<br>2. EORTC PC module | None | -- | None | None | -- | None |
| SEUG 9901[28] | 2014 | 1. QLQ-C30<br>2. EORTC PC module | Hot flushes gynecomastia<br>Leg swelling<br>Sexual function | -- | None | Hot flushes<br>Gynecomastia<br>Headaches | -- | None |
| Verhagen et al.[29] | 2014 | QLQ-C30 | Physical<br>Emotional | -- | Cognitive | Fatigue<br>Diarrhea<br>Nausea & vomiting<br>Constipation<br>Hot flushes<br>Financial worry<br>Gynecomastia | -- | None |
| ICELAND[30] | 2016 | QLQ-C30 | None | -- | None | None | -- | None |

**Table 3. Quality of life and adverse effects in randomized trials of IAD vs. CAD.**

Abbreviations: EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC PC module=EORTC prostate cancer-specific questionnaire; PC=prostate cancer

| Clinicaltrials.gov identifier | Phase | Treatment | Primary Endpoint | Status | Estimated primary completion date |
|---|---|---|---|---|---|
| **NCT02677896** | III | Enzalutamide/placebo plus ADT | Radiographic PFS | Active, not recruiting | Q4-2018 |
| **NCT01957436** | III | ADT and 6 cycles of docetaxel +/- abiraterone acetate +/- local radiotherapy | OS and PFS | Recruiting | Q4-2018 |
| **NCT02649855** | III | 6 cycles of docetaxel and 4-6 injections of PROSTVAC before, during or after docetaxel in addition to standard ADT | Response score | Recruiting | Q1-2020 |
| **NCT02489318** | III | Apalutamide/placebo and ADT | Radiographic PFS | Active, not recruiting | Q4-2020 |
| **NCT02799602** | III | Darolutamide/placebo, standard ADT and 6 cycles of docetaxel | OS | Active, not recruiting | Q3-2022 |

**Table 4. Select ongoing trials of frontline therapy in metastatic castration-sensitive prostate cancer.**

Abbreviations: ADT=androgen deprivation therapy; OS=overall survival; PFS=progression-free survival

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