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Platinum Priority – Prostate Cancer – Editor's Choice

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Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial

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Abstract

Background: Long-term androgen deprivation therapy (ADT) combined with radiotherapy (RT) is a standard treatment for patients with localized high-risk prostate cancer (HRPC). However, the optimal duration of ADT is not yet defined.
Objective: The aim of this superiority randomized trial was to compare outcomes of RT combined with either 36 or 18 mo of ADT.
Design, setting and participants: From October 2000 to January 2008, 630 patients with HRPC were randomized, 310 to pelvic and prostate RT combined with 36 mo (long arm) and 320 to the same RT with 18 mo (short arm) of ADT.
Outcome measurements and statistical analysis: Overall survival (OS) and quality of life (QoL) were primary end points. OS rates were compared with Cox Regression model and QoL data were analyzed through mixed linear model.
Results and limitations: With a median follow-up of 9.4 yr, 290 patients had died (147 long arm vs 143 short arm). The 5-yr OS rates (95% confidence interval) were 91% for long arm (88–95%) and 86% for short arm (83–90%), $p = 0.07$. QoL analysis showed a significant difference ($p < 0.001$) in six scales and 13 items favoring 18 mo ADT with two of them presenting a clinically relevant difference in mean scores of $\geq$10 points.
Conclusions: In localized HRPC, our results support that 36 mo is not superior to 18 mo of ADT. ADT combined with RT can potentially be reduced to 18 mo in selected men without compromising survival or QoL. Thus, 18 mo of ADT appears to represent a valid option in HRPC.
Patient summary: In this study, we report outcomes from high-risk prostate cancer patients treated with radiotherapy and either 36 or 18 mo of androgen deprivation therapy. There was no difference in survival between the two groups, with the 18-mo group experiencing a better quality of life.

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1. Introduction

In high-risk prostate cancer (HRPC), the addition of 36 mo of androgen deprivation therapy (ADT) to radiotherapy (RT) improves overall survival (OS) over either RT [1] or ADT [2] alone. However, the optimal duration of ADT remains undefined. Long-term ADT can be associated with important toxicity [3,4], potentially impairing quality of life. Thus, attempts to reduce these potential toxicities by decreasing the total duration of ADT administration without compromising outcomes are under investigation. A superiority randomized trial comparing 36 mo versus 6 mo of ADT showed an inferior survival for the shorter ADT arm [5]. We report results of a phase III trial comparing 36 mo with 18 mo of ADT in HRPC patients treated with RT.

2. Material and methods

Prostate cancer study IV (ClinicalTrials.gov Identifier NCT00223171) was a phase III prospective, multicenter randomized trial for patients with localized HRPC. HRPC was defined as American Joint Committee on Cancer [6] clinical stage T3–T4 (based on digital examination), or a prostate-specific antigen (PSA) >20 ng/ml or a Gleason score >7. Any patient with at least one of the three risk factors was eligible to participate in the study. The Ethics Review Board of each institutional approved the study protocol. AstraZeneca Pharmaceuticals funded the study and was not involved in any step of the trial.

2.1. Inclusion criteria

Inclusion criteria were histologically-proven HRPC, Zubrod ≤1, age ≤80 yr, and no evidence of regional or metastatic disease. All patients gave written, informed consent prior to participating in the study.

2.2. Staging and follow-up procedures

Evaluation included history and physical examination, assessment of sexual function, complete blood counts, PSA level, serum testosterone, and liver function tests, computed tomography scan or magnetic resonance imaging of the abdomen and pelvis, and bone scan. Clinical assessment and laboratory testing were repeated every 3 mo for the first 18 mo, every 6 mo up to 3rd yr and yearly thereafter until death or end of the study.

2.3. Study design and treatment

Our trial was planned in 1998–1999 after the first release of the European Organization for Research and Treatment of Cancer (EORTC) randomized study 22 863 in 1997 [1] showed a significant improved 5-yr OS rate favoring the combination of ADT for 36 mo plus RT versus RT alone for patients with HRPC.

From October 2000 to January 2008, HRPC patients were randomized between a standard arm of RT and 36 mo of ADT (long arm) and the experimental arm of RT and 18 mo of ADT (short arm). Stratified randomization was performed controlling for PSA ≥20 ng/ml versus <20 ng/ml, stage T3–T4 versus T1–T2, and Gleason score <7 versus ≥8, resulting in eight blocks. From each block, a simple randomization (1:1) was realized using lists of random numbers. Patients were registered and randomized by the data center. The assigned treatment was generated by the randomization program and the participating center informed immediately by fax.

Prior to RT, all patients received 4 mo of a luteinizing hormone-releasing hormone agonist (LHRHa; goserelin acetate depot 10.8 mg, Zoladex) and an anti-androgen (bicalutamide, Casodex) given orally at a dose of 50 mg daily for 1 mo. LHRHa was continued during and after RT for a total duration of either 36 or 18 mo with continuous toxicity evaluation.

RT using three-dimensional conformal techniques was identical in both arms. Patients received a dose of 44 Gy in 22 fractions to the whole pelvis and 70 Gy in 35 fractions to the prostate. Acute toxicity was assessed with the Common Terminology Criteria for Adverse Events version 2.0 and late toxicity with the use of the Radiation Therapy Oncology Group (RTOG)/EORTC criteria [7].

Quality of life (QoL) was assessed by two EORTC validated tools: EORTC30 version 3.0 is a 30-item scoring scale for global QoL and PR25 more specific to prostate cancer. PR25 consists of 25 items, and six of them assess sexual activity and sexual functioning (SF). SF evaluation is conditional to the patient being sexually active 4 wk prior to the evaluation. All 55 items were regrouped into 21 scales. Patient-reported outcome questionnaires were filled out before treatments, every 6 mo during ADT and then once a year for 5 yr.

2.4. End points

Primary end points were OS and QoL at 5 yr. Secondary end points were biochemical failure (BF), defined as PSA nadir plus 2, site of tumor relapse and disease-free survival (DFS).

Table 1 – Patient characteristics at study entry

	Long arm (36 mo) n = 310	Short arm (18 mo) n = 320
Age (yr)		
Median	71	71
Range	51–80	51–80
IQR	67–74	65–74
Zubrod performance scales, n (%)		
0	268 (87)	288 (90)
1	42 (14)	32 (10)
Pre-existing co-morbidities, n (%)		
Cardiac disease [a]	86 (28)	98 (31)
Hypertension [b]	159 (51)	150 (47)
Diabetes [b]	54 (17)	56 (18)
Chronic obstructive pulmonary disease [a]	29 (9.4)	31 (10)
Clinical tumor stage (AJCC 1997), n (%)		
T1c	76 (25)	80 (25)
T2a	58 (19)	64 (20)
T2b	78 (25)	80 (25)
T2c	18 (5.8)	24 (7.5)
T3a	70 (23)	57 (18)
T3b	10 (3.2)	13 (4.1)
T4	0 (0)	2 (0.6)
Gleason score, n (%)		
6	40 (13)	44 (14)
7	87 (28)	83 (26)
8	121 (39)	128 (40)
9	55 (18)	62 (19)
10	7 (2.3)	3 (0.9)
PSA (ng/ml)		
PSA > 20 ng/ml	142 (46)	137 (43)
Median	16.4	15.4
Range	1.1–153.0	0.6–252.0
IQR	8.6–28.2	8.4–28.1

AJCC = American Joint Committee on Cancer 1997 (Cancer Staging Manual, Fifth Edition); IQR = interquartile range; PSA = prostate-specific antigen (upper limit of the normal range = 4 ng/ml).
[a] Two patients with missing data, one in each arm.
[b] One patient with missing data in the short arm.

2.5. Statistical analysis

The trial was designed assuming a survival difference of 9% between arms at 5 yr (79% for 36 mo and 70% for 18 mo) with a constant hazard ratio (HR) of 1.5. For an 80% power to detect this difference with a 0.050 level, one-sided log-rank test [8], 303 patients per arm were required. Accounting for a 5% patient ineligibility or drop out, we calculated a total sample size of 630 patients. Statistical analyzes were done only on the available data. No imputation was done for the missing data.

Patient characteristics were evaluated with frequencies and percentages for categorical variables or with median and interquartile range (IQR: 25th–75th percentiles) for continuous variables. Analysis was by intention to treat in all patients randomly assigned to the two treatment arms. SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA), R version 3.3.2 software (R Development Core Team, 2008) and GrapPad Prism version 7.00 software

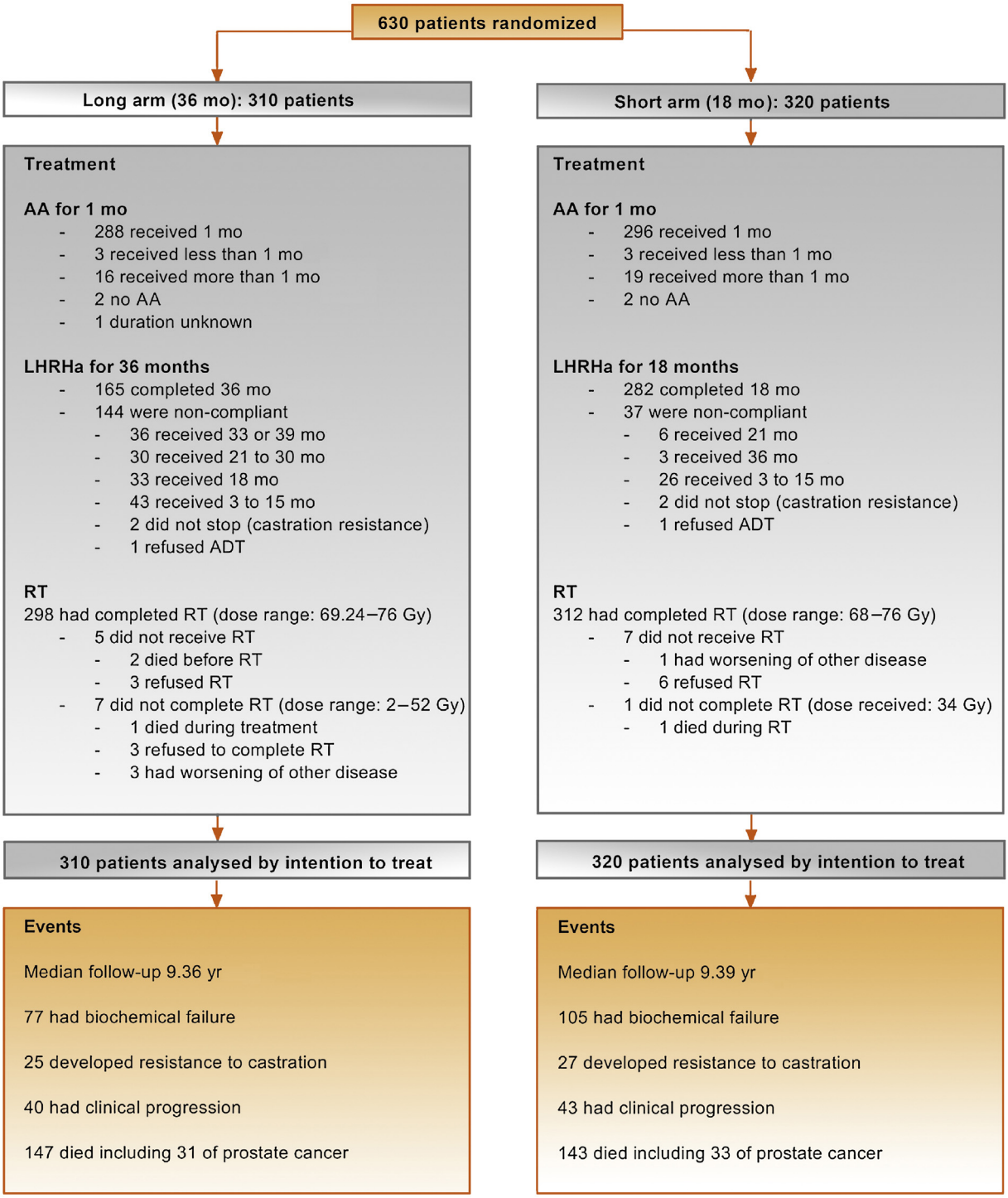

Fig. 1 – Enrollment and follow-up of study patients.
AA = anti-androgen; ADT = androgen deprivation therapy; Gy = Gray; LHRHa = luteinizing hormone-releasing hormone agonist; RT = radiotherapy.

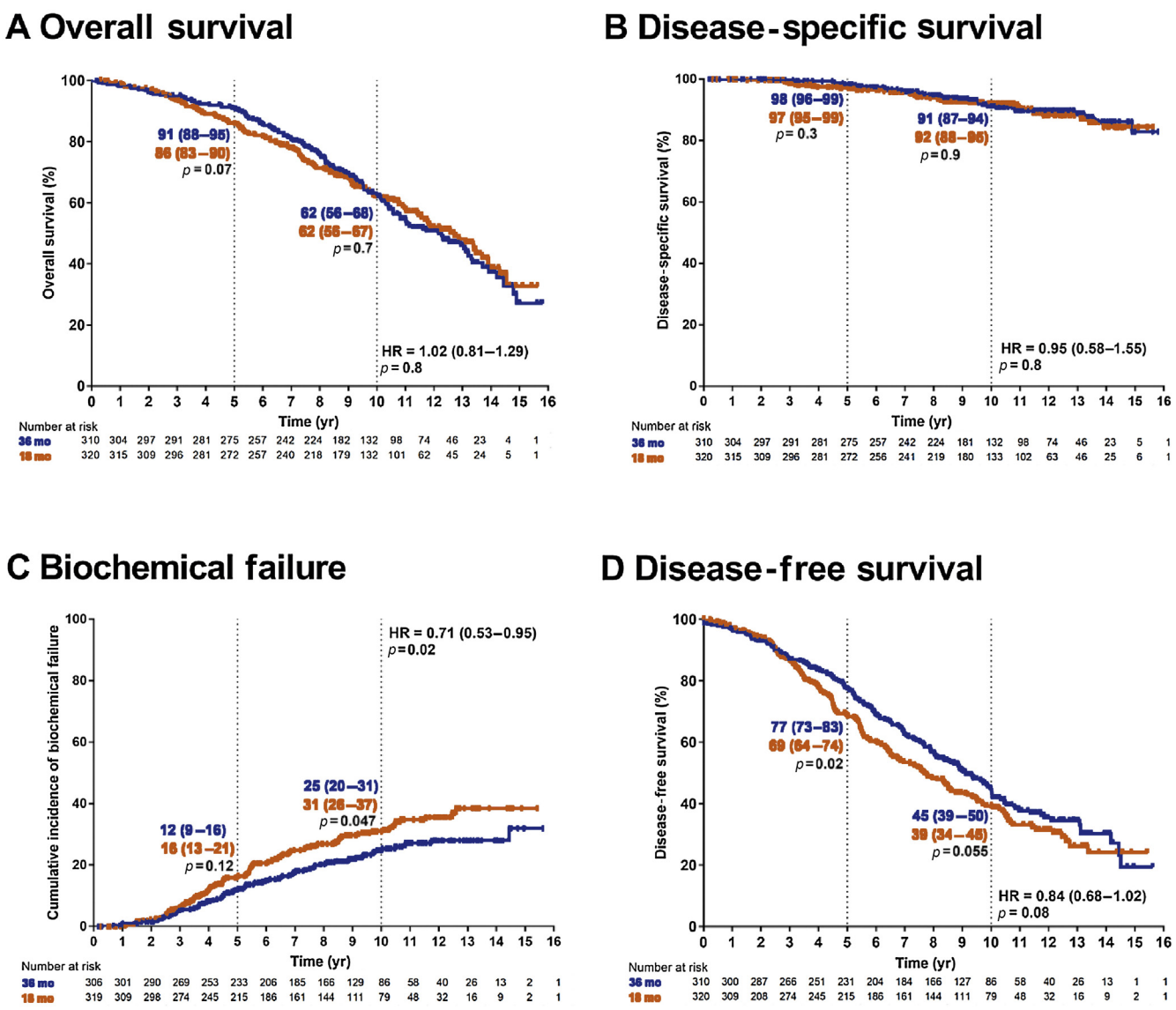

Fig. 2 – Survival and biochemical failure rates between long arm (36 mo) and short arm (18 mo).
HR = hazard ratio with 95% confidence intervals.
HR compared between 36 mo and 18 mo.

(GraphPad Software Inc., La Jolla, California, USA) were used. OS and DFS rates were estimated by the Kaplan-Meier method and were compared between arms with a log-rank test. HRs and confidence intervals (CIs) were estimated through Cox Regression model. The proportional hazards assumption was validated with the Kolmogorov-type supremum test [9]. Multivariable Cox regression was used to evaluate factors associated with OS. BF, site of tumor relapse, and disease-specific survival (DSS) were analyzed with sub distribution analysis of competing risks methods [10,11]; p value less than 0.05 was considered significant.

For the QoL assessment, EORTC30 and PR25 items were transformed into scales according to the EORTC guidelines [12]. All items and scales scores were linearly transformed to a 0–100 points scale. Means and standard deviation of scales and items for each group at each time point were estimated. Mixed linear model with repeated measures were used to compare randomized groups over time. A p value <0.01 was considered statistically significant to account for multiple comparisons and a difference between groups in mean scores of ≥ 10 points as clinically relevant [13].

3. Results

3.1. Patient characteristics

The arms were well balanced for age, pre-existing co-morbidities, Zubrod performance scale, Gleason score, PSA level, clinical stage, and risk factors distribution (Table 1).

3.2. Adherence to ADT and RT

The median duration of ADT for all patients was 35.4 mo (IQR: 19.8–35.9) for the long arm and 17.9 months (IQR: 17.6–18.1) for the short arm. Prescribed duration of ADT, including all patients, was reached more often for 18 mo arm (282/320, 88%) than 36 mo (165/310, 53%). Further details of ADT duration are shown in Fig. 1 and Supplementary

Table 2 – Univariable and multivariable Cox Regression analysis for overall survival

	Univariable		Multivariable (ITT)		Multivariable (PP) [a]		Multivariable Landmark model [b]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
36 vs 18 mo (ITT)	1.02 (0.81–1.29)	0.8	0.92 (0.65–1.3)	0.6	–	–	–	–
36 vs 18 mo (PP)	0.97 (0.72–1.30)	0.8	–	–	0.86 (0.6–1.24)	0.4	–	–
ADT duration (mo) [b]	1.00 (0.99–1.02)	0.6	–	–	–	–	1.00 (0.99–1.02)	0.7
Age (yr)	1.05 (1.03–1.07)	<0.001	1.05 (1.02–1.08)	0.002	1.06 (1.02–1.09)	<0.001	1.05 (1.02–1.07)	<0.001
Gleason 8–10	1.40 (1.10–1.78)	0.006	1.21 (0.81–1.81)	0.3	1.18 (0.74–1.9)	0.5	1.43 (1.02–2.01)	0.041
T3–T4 stage	1.04 (0.80–1.36)	0.8	1.38 (0.96–2)	0.08	1.33 (0.85–2.09)	0.2	1.36 (0.99–1.86)	0.057
PSA >20 ng/ml	0.88 (0.70–1.11)	0.3	0.97 (0.66–1.43)	0.9	1.04 (0.66–1.65)	0.9	1.02 (0.74–1.42)	0.9

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; PP = per protocol; PSA = prostate-specific antigen.
[a] Per protocol analysis was performed only with patients who completed 36 mo (n = 168) and 18 mo (n = 315) of ADT.
[b] The landmark model considers the ADT duration in months and starting at 36 mo of follow-up. Patients who had died before 36 mo were excluded, and only patients with at least 18 mo of ADT were included (n = 533).

Figure 1. Causes of noncompliance for ADT for 36 and 18 mo were: side effects 70 versus 10, patient's refusal to continue 18 versus 1, other disease or medical reason 14 versus 1, death 11 versus 7, institutional or patient error 9 versus 8, prostatectomy 1 versus 2, castrate resistance 2 versus 2, withdrawal from study 3 versus 1, lost to follow-up 3 versus 1, unknown 13 versus 1, respectively, and finally three patients in short arm continued ADT for 36 mo. Adherence to RT was good and similar in both arms, 96% versus 98% for long and short arm, respectively.

3.3. OS, DSS, and causes of death

After a median follow-up of 9.4 yr, 290 patients had died (147 long arm vs 143 short arm). Median follow-up for patients who survived was 10.6 yr (IQR: 9.1–12.6). The 5-yr OS actuarial rates (95% CI) were 91% (88–95%) and 86% (83–90%) for 36 and 18 mo, respectively, and p = 0.07. The 10-yr OS actuarial rates were 62% (56–67%) and 62% (56–67%) for 36 and 18 mo, respectively, p = 0.7, and the global HR (95% CI) of 1.02 (0.81–1.29), p = 0.8 (Fig. 2A). The 5- and 10-yr actuarial DSS rates were similar for 36 and 18 mo (Fig. 2B). Causes of death for 36 and 18 mo were: a second malignancy in 35 patients (24%) versus 40 (28%), prostate cancer 31 (21%) versus 33 (23%), cardiovascular disease 25 (17%) versus 25 (18%), pulmonary disease 22 (15%) versus 17 (12%), digestive disease 4 (2.7%) versus 5 (3.5%), other causes 20 (14%) versus 15 (11%), and unknown 10 (6.8%) versus 8 (5.6%), respectively.

Univariable and multivariable Cox Regression analysis for OS showed that only age and Gleason score >7 were statistically significant survival predictors. Duration of ADT, T3-T4 stage, and PSA >20 ng/ml were not predictive of OS in intention to treat, per protocol analysis and by a landmark model analysis (Table 2).

A post hoc subgroup analysis including only patients with Gleason 8–10 performed for OS, DSS, BF, DFS, and the development of distant metastases shows no significant difference in any of these variables between the arms (Supplementary Fig. 2). We also run regressions with interaction between ADT duration and Gleason 8–10 versus 7 or less for OS, DFS, DSS, and BF and found no significant differences (Supplementary Table 1).

3.4. BF and metastases

In total, 182 patients had BF (77 in long arm vs 105 in short arm). The cumulative incidence of BF at 10 yr was 25% (20–31%) for 36 mo as compared with 31% (26–37%) for 18 mo (global adjusted HR for competing risks = 0.71 (0.53–0.95), p = 0.02 (Fig. 2C). Of the 182 patients developing BF, 44 (24%) did not receive a second course of ADT. The rate of exposure to a second course of ADT post BF was similar between the arms.

Furthermore, 83 patients developed prostate cancer disease progression (40 in long arm vs 43 in short arm). Site of distant metastases was mainly bone with no difference between arms (Table 3). Also, 52 patients (25 long arm vs 27 short arm) became castrate-resistant. The 10-yr DFS actuarial rates were 45% (39–50%) and 39% (34–45%) for 36 and 18 mo, respectively, with a global HR of 0.84 (0.68–1.02), p = 0.08 (Fig. 2D). A forest plot is available in the supplementary material (Supplementary Fig. 3).

3.5. Toxicity

ADT toxicity was high for hot flushes, erectile dysfunction, fatigue, and gynecomastia (Supplementary Fig. 4). Acute and late toxicities attributed to RT were similar between the arms (Supplementary Table 2 and Supplementary Fig. 5).

Table 3 – Site of tumor relapse

	Long arm (36 mo)	Short arm (18 mo)	Total
Prostate alone	3	4	7
Prostate + metastasis	2	0	2
Pelvic nodes alone	0	1	1
Pelvic nodes + metastasis	1	3	4
Bone alone	23	24	47
Bone + other locations	11	11	22
Total	40	43	83

Table 4 – Quality of life results

	Baseline		End of QoLQ		Overall *p* value
			8 yr	6.5 yr	
	36 mo (*n* = 269) Mean ± SD	18 mo (*n* = 273) Mean ± SD	36 mo (*n* = 170) Mean ± SD	18 mo (*n* = 178) Mean ± SD	
Global QoL	78.0 ± 20.2	77.9 ± 20.1	74.8 ± 20.5	76.6 ± 19.3	0.3
Overall health (Q29)	77.4 ± 20.1	76.3 ± 21.9	74.5 ± 20.3	76.0 ± 20.0	0.3
Overall quality of life (Q30)	78.6 ± 21.6	79.5 ± 20.5	75.0 ± 21.9	77.3 ± 20.1	0.2
Physical	90.4 ± 13.8	91.1 ± 14.5	82.8 ± 19.8	86.0 ± 19.7	<**0.001**
Trouble to do physical effort (Q1)	85.9 ± 24.4	86.7 ± 25.8	73.1 ± 33.5	80.3 ± 31.8	0.012
Trouble to take a long walk (Q2)	75.7 ± 32.3	79.5 ± 31.2	62.2 ± 37.3	68.9 ± 37.4	<**0.001**
Trouble to take a short walk outside (Q3)	95.4 ± 14.1	95.2 ± 16.3	88.6 ± 23.2	89.3 ± 23.6	0.2
Need to stay in bed or chair (Q4)	95.3 ± 15.3	95.1 ± 15.1	91.7 ± 19.5	92.9 ± 20.0	**0.005**
Need help eating, dressing, washing, and toilet (Q5)	99.8 ± 2.9	99.1 ± 8.8	98.4 ± 10.1	98.3 ± 9.6	0.5
Role	93.6 ± 15.8	92.1 ± 18.3	85.3 ± 26.4	86.3 ± 26.0	0.5
Limited to do work or daily activities (Q6)	94.7 ± 15.5	92.6 ± 18.9	85.5 ± 27.6	87.1 ± 25.3	1
Limited in pursuing hobbies or leisure time activities (Q7)	92.4 ± 18.3	91.8 ± 19.9	85.2 ± 27.7	85.6 ± 28.3	0.2
Emotional	81.7 ± 20.9	82.5 ± 20.0	88.2 ± 18.2	88.8 ± 15.1	<**0.001**
Feel tense (Q21)	81.5 ± 23.6	81.9 ± 23.4	87.5 ± 21.7	88.1 ± 19.2	**0.001**
Worry (Q22)	76.2 ± 26.7	77.9 ± 25.8	86.3 ± 23.9	85.9 ± 20.9	<**0.001**
Feel irritable (Q23)	84.1 ± 23.7	84.9 ± 23.2	89.2 ± 19.4	90.0 ± 18.3	0.01
Feel depressed (Q24)	85.0 ± 24.3	85.2 ± 22.3	90.0 ± 22.3	91.1 ± 16.8	**0.002**
Cognitive	89.8 ± 14.8	87.7 ± 17.3	87.0 ± 17.7	87.3 ± 18.1	0.7
Difficulty with concentration (Q20)	93.9 ± 15.5	93.4 ± 16.8	92.4 ± 17.8	93.2 ± 16.8	0.02
Difficulty to remember things (Q25)	85.7 ± 19.1	82.1 ± 23.9	81.5 ± 24.4	81.4 ± 23.8	0.2
Social	93.9 ± 14.8	95.6 ± 12.6	91.8 ± 20.9	94.4 ± 16.4	**0.009**
Physical condition or medical treatment interfered with family life (Q26)	93.1 ± 18.0	96.1 ± 12.8	93.1 ± 19.9	95.5 ± 15.2	0.02
Physical condition or medical treatment interfered with social activities (Q27)	93.1 ± 18.0	96.1 ± 12.8	93.1 ± 19.9	95.5 ± 15.2	0.02
Fatigue	15.6 ± 19.7	14.5 ± 17.9	19.5 ± 22.3	16.9 ± 19.3	**0.003**
Need to rest (Q10)	17.2 ± 22.4	16.8 ± 22.7	22.8 ± 26.1	21.2 ± 24.7	0.02
Felt weak (Q12)	12.8 ± 22.3	11.0 ± 19.4	14.8 ± 24.6	11.2 ± 20.3	<**0.001**
Felt tired (Q18)	17.0 ± 23.0	15.7 ± 20.4	20.4 ± 25.9	18.3 ± 24.1	0.04
Nausea and vomiting	1.2 ± 5.1	1.2 ± 5.4	1.7 ± 6.2	1.0 ± 4.4	0.04
Nausea (Q14)	2.0 ± 8.4	2.2 ± 9.7	2.9 ± 11.4	1.5 ± 6.9	0.02
Vomiting (Q15)	0.2 ± 2.9	0.2 ± 2.8	0.4 ± 3.6	0.6 ± 4.3	0.6
Pain	8.6 ± 16.5	9.8 ± 17.9	13.0 ± 23.5	9.7 ± 19.2	0.5
Had pain (Q9)	10.0 ± 20.6	12.2 ± 23.2	13.7 ± 25.3	10.3 ± 21.8	0.7
Pain interfered with daily activities (Q19)	6.9 ± 15.8	7.3 ± 17.9	12.4 ± 24.8	9.1 ± 20.3	0.4
Dyspnea/short of breath (Q8)	17.1 ± 26.6	17.3 ± 25.5	22.0 ± 29.7	21.5 ± 29.3	0.4
Insomnia/trouble sleeping (Q11)	19.8 ± 26.4	18.9 ± 25.5	16.3 ± 24.7	15.7 ± 26.3	0.9
Appetite loss (Q13)	5.1 ± 15.6	3.3 ± 11.5	5.3 ± 15.1	3.2 ± 12.1	0.12
Constipation (Q16)	10.0 ± 20.4	10.3 ± 21.0	9.4 ± 19.6	9.6 ± 20.5	0.03
Diarrhea (Q17)	4.6 ± 12.9	6.7 ± 18.3	9.6 ± 21.0	5.5 ± 14.3	0.14
Financial difficulties (Q28)	5.5 ± 15.6	6.0 ± 17.2	4.7 ± 17.1	2.6 ± 11.5	0.4
Urinary	15.8 ± 15.2	16.1 ± 15.2	13.4 ± 16.4	13.5 ± 15.1	0.2
Urinate frequently during the day (Q31)	37.0 ± 29.6	36.5 ± 31.3	24.3 ± 29.6	25.0 ± 29.3	0.8
Urinate frequently at night (Q32)	32.8 ± 29.2	33.2 ± 28.8	27.5 ± 28.6	29.9 ± 28.5	0.7
Urge to pass urine, hurry to get to the toilet (Q33)	18.8 ± 28.7	18.8 ± 27.8	16.1 ± 27.2	16.7 ± 26.7	0.05
Difficult to get enough sleep: get up frequently at night to urinate (Q34)	12.1 ± 23.6	13.9 ± 23.6	11.2 ± 21.7	12.3 ± 22.7	0.13
Difficult going out of the house because need to be close to a toilet (Q35)	6.5 ± 17.3	6.3 ± 16.7	9.0 ± 21.4	7.0 ± 17.7	<**0.001**
Unintentional release (leakage) of urine (Q36)	9.3 ± 18.2	9.6 ± 19.0	10.3 ± 19.6	10.2 ± 20.4	0.09
Pain when urinated (Q37)	6.2 ± 16.4	6.6 ± 16.6	2.2 ± 10.3	1.7 ± 10.2	0.9
Limited daily activities by urinary problems (Q39)	3.3 ± 13.2	4.0 ± 11.9	5.9 ± 18.8	4.3 ± 14.3	0.05
Bowel	2.9 ± 6.7	3.6 ± 7.8	6.7 ± 13.0	5.0 ± 9.7	0.4
Limited daily activities by bowel problems (Q40)	2.0 ± 9.8	2.2 ± 10.5	6.1 ± 18.5	5.1 ± 17.0	0.3
Unintentional release (leakage) of stools (Q41)	0.6 ± 4.5	2.1 ± 8.6	9.1 ± 19.9	5.5 ± 13.9	0.7
Blood in stools (Q42)	1.0 ± 6.4	1.2 ± 6.3	2.0 ± 8.8	2.2 ± 9.0	**0.003**
Bloated feeling in the abdomen (Q43)	7.9 ± 18.7	8.8 ± 19.3	9.7 ± 20.5	7.5 ± 15.3	0.6
Treatment	7.3 ± 9.8	7.8 ± 10.3	10.4 ± 13.0	9.9 ± 11.6	<**0.001**
Hot flushes (Q44)	8.8 ± 20.8	9.0 ± 20.7	14.3 ± 25.3	13.3 ± 24.4	<**0.001**
Sore or enlarged nipples or breasts (Q45)	1.1 ± 6.7	1.0 ± 5.7	4.7 ± 14.7	3.7 ± 13.8	<**0.001**
Swelling in legs or ankles (Q46)	5.9 ± 15.7	6.9 ± 17.1	11.1 ± 23.1	9.2 ± 19.9	0.3
Weight loss been a problem (Q47)	10.4 ± 23.9	9.8 ± 22.2	10.1 ± 24.6	10.3 ± 23.7	0.2
Weight gain been a problem (Q48)	7.2 ± 20.1	9.3 ± 23.0	8.7 ± 22.5	7.1 ± 18.8	0.2
Felt less masculine because of illness or treatment (Q49)	10.4 ± 21.7	10.5 ± 21.5	13.2 ± 26.5	15.6 ± 25.5	0.4
Sexual activity	27.8 ± 27.3	28.4 ± 26.9	12.2 ± 18.6	15.5 ± 23.7	<**0.001**

Table 4 (*Continued*)

	Baseline		End of QoLQ		Overall *p* value
			8 yr	6.5 yr	
	36 mo (*n* = 269) Mean ± SD	18 mo (*n* = 273) Mean ± SD	36 mo (*n* = 170) Mean ± SD	18 mo (*n* = 178) Mean ± SD	
Interested in sex (Q50)	34.7 ± 32.2	35.0 ± 32.0	16.1 ± 24.7	19.4 ± 28.9	<**0.001**
Sexually active (with or without intercourse) (Q51)	20.9 ± 28.4	21.7 ± 27.9	8.3 ± 17.4	11.6 ± 23.7	<**.0001**
Sexual functioning [a]	70.0 ± 23.2	69.4 ± 24.6	55.3 ± 21.7	62.8 ± 23.2	**0.03**
Sex enjoyable (Q52) [a]	60.9 ± 32.2	64.2 ± 29.9	48.5 ± 22.2	59.2 ± 30.7	**0.001**
Difficulty to get or maintain an erection (Q53) [a]	62.1 ± 35.4	59.3 ± 34.7	48.5 ± 29.0	47.0 ± 36.4	0.5
Ejaculations problems (Q54) [a]	73.0 ± 35.7	71.6 ± 36.3	53.5 ± 32.2	64.1 ± 37.0	0.4
Felt uncomfortable about being sexually intimate (Q55) [a]	83.9 ± 30.2	82.2 ± 31.0	70.7 ± 36.1	79.5 ± 32.1	0.14

QoLQ = quality of life questionnaire; SD = standard deviation.
Scales were in bold and associated items were listed below and were staggered.
Item about wearing an incontinence aid is a problem (Q38) was not presented in the table because there are no sufficient patients (<10 patients by arm).
A *p* value < 0.01 was considered statistically significant to account for multiple comparisons (in bold).
[a] The number of patients for 36 and 18 mo were: 110 and 122 at baseline, 17 and 61 at 2.5 yr, and 33 and 39 at the end of QoLQ, respectively.
For scales about function (Global QoL, Physical, Role, Emotional, Cognitive, Social) and corresponding items, 0 indicates the lowest function and 100 the best. For scales about symptoms (Fatigue, Nausea and vomiting, Pain, Urinary, Bowel, Treatment, Sexual activity, Sexual functioning) and corresponding items, 0 indicates the fewest symptoms and 100 the most.

3.6. *Quality of life*

Global adherence to QoL questionnaires (QoLQ) was 72%. QoLQ adherence rates were 87% versus 85% at baseline for 36 versus 18 mo, respectively, and 55% versus 56% 5 yr after the end of ADT. Results from the multi-trait scaling and scoring analysis are shown in Table 4. There was no statistical difference in global QoL between arms, $p = 0.3$ (Fig. 3A). However, six out of 21 scales (physical, emotional, and social functioning, fatigue, hormonal treatment-related symptoms, and sexual activity) and 13 out of 55 items (trouble with long walk, stay in bed during the day, weakness, tenseness, worry, depressed, close to a toilet, blood in stools, hot flushes, enlarged breasts, interested in sex, sexually active, enjoyable sex) were statistically significant ($p < 0.01$) in favor of the 18-mo ADT arm. None of the 21 scales reached clinical relevance, sexual activity being the highest score with 9.0 points of difference at 2.5 yr. For the 13 statistically significant items, interest in sex with 9.9 points at 2.5 yr was close to clinical relevance. Hot flushes with 23.9 points and enjoyable sex with 18.6 points had important clinical relevance at 3.5 yr (Fig. 3B–E and Supplementary Fig. 6).

3.7. *Testosterone recovery*

A significantly higher percentage of patients (58%) in the 18-mo ADT group recovered a normal testosterone level compared with the 36-mo ADT group (48%), $p = 0.02$. Moreover, testosterone recovery measured from the date of randomization was significantly faster for 18 mo than for 36 mo: median time (95% CI) 3.6 (3.1–4.2) versus 6.6 (5.2–8.0) yr, $p < 0.001$ (Fig. 3F). Testosterone recovery was also significantly faster for the 18 mo when measured from the end of ADT (median time: 2.1 vs 4.0 yr, $p = 0.02$). In patients remaining with a castrate testosterone level, the rate of BF was similar between arms: 20% (31/153) in 36 mo and 23%, (29/124) in 18 mo, $p = 0.5$. The rate of BF after normal testosterone recovery was significantly higher in the short arm (38% vs 27%, $p = 0.04$).

4. Discussion

Two EORTC and one RTOG randomized trials have shown improvement in OS in HRPC patients treated with RT and 36 mo of ADT compared with either no ADT [14] or only 6 mo of ADT [5] or 28 mo versus 4 mo of ADT (RTOG 9202) [15]. When compared with the EORTC trials, our study, with a more recent recruitment period (2000–2008), is characterized by fewer patients with stage T3–T4 but with a higher proportion of patients with Gleason score 8–10 and a similar median PSA level. Although there was a significant increase in biochemical control in 36 mo, likely due to a longer duration of ADT and a faster testosterone rebound in the shorter ADT arm, it did not translate into a significant advantage for the other outcomes, including local failure rate, DFS, DSS, resistance to castration, development of metastases, or OS. A word of caution is necessary when applying these results universally to younger patients because it is conceivable that this difference in PSA failure could translate into a difference in OS or another end point with a longer follow-up and a lower death rate from causes outside prostate cancer.

The trial was designed as a superiority trial with the conception of a potential trade-off between a higher OS for the 36-mo ADT arm (a difference of 9%) in return of a better QoL for the 18-mo arm. Preliminary results with a median follow-up of 6.4 yr showed no survival difference between arms [16], indicating a lack of superiority for the 36-mo ADT arm. However, the HR upper bound at 1.56 for OS (HR [95% CI] = 1.15 [0.85–1.56], $p = 0.4$) was considered far too high to establish a non-inferiority outcome. By adopting the same upper bound limit of 1.35 defined by the EORTC study [5], 275 death events were estimated necessary to achieve a similar HR upper bound limit in our study. With a median

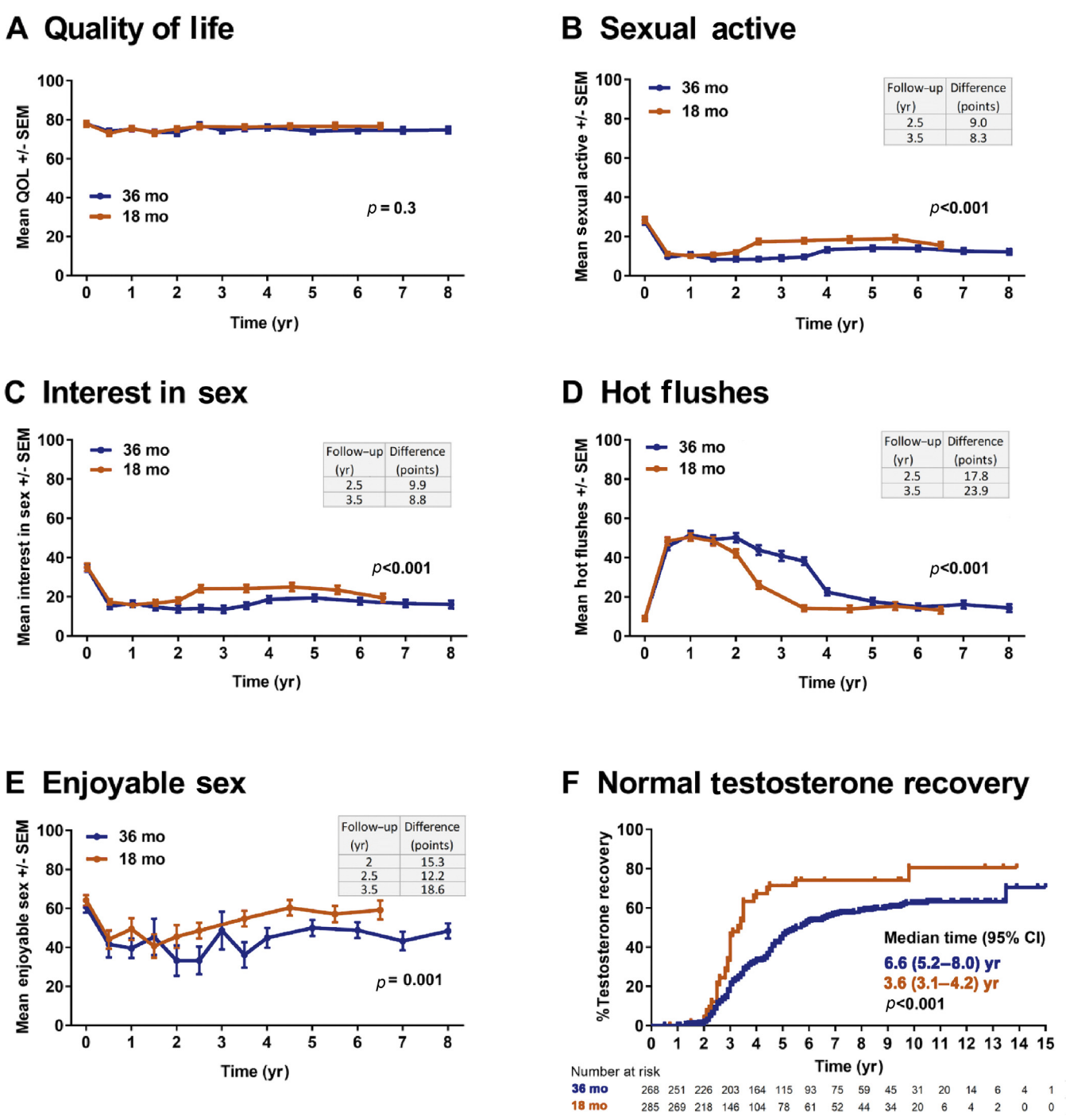

Fig. 3 – Mean scores on quality of life assessment scales or items and time to normal testosterone level recovery. The mean scores were presented for global quality of life (A) (0 indicate no QoL and 100 high QoL), and sexual activity (B) (0 indicate no sexual activity and 100 high sexual activity). Other items: (C) interest in sex (0 indicate no interest and 100 high interest), (D) hot flushes (0 indicate no symptoms and 100 severe symptoms), (E) enjoyable sex (0 indicate no enjoyable and 100 high enjoyable). (F) Time to normal testosterone recovery. A *p* value < 0.01 was considered statistically significant to account for multiple comparisons and a difference between groups in mean scores of ≥10 points as clinically relevant.
CI = confidence interval; QoL = quality of life.

follow-up of 9.4 years and 290 death events, results still show no statistical difference in OS between arms at 5 yr. We acknowledge that a power higher than 80% could provide more robust results.

Although this study was not designed as a non-inferiority trial, based on the current number of events, focusing on a post hoc analysis of the data beyond 5 yr, performing a per protocol outcome analysis (Table 2), and using an upper bound limit below 1.35 (HR = 1.02 [0.81–1.29]), it is conceivable that 18 mo of ADT is not inferior to 36 mo when combined with RT for the treatment of HRPC for the end point of death;

however, this must still be viewed as speculative and not definitive.

Similar to the EORTC trial of 6 versus 36 mo of ADT, there was no difference in global QoL. Nevertheless, six scales and 14 items showed a significant difference favoring 18 mo, and in two items (hot flushes and enjoyable sex), this difference was clinically relevant. The better QoL profile in the 18-mo arm can be attributed to a faster testosterone recovery [14].

Few aspects of our study warrant further discussion. First, at the time of trial design, 70 Gy was considered a standard RT dose for patients with high-risk disease and was the dose used in previous randomized trials [1,2,17]. With the development of newer RT techniques and brachytherapy that permit the safe delivery of higher doses of radiation, it is conceivable that "dose-escalated" RT could lead to further benefits in terms of biochemical control, as it has been shown in previous randomized trials [18–21]. Second, only 53% of patients in the long arm completed the 36 mo of ADT. Although this percentage can be perceived as low, it relates to the overall compliance not excluding patients who stopped the ADT because of disease progression, medical reasons, severe side effects, or death. If all these factors are taken into account, this rate of compliance is consistent with other trials using similar or longer ADT duration [1,22] even though it is still lower than the compliance rate of EORTC 22961 study [5] in which 72% of patients completed 3 yr of ADT. This lower ADT compliance rate may hinder the interpretation of our results.

5. Conclusions

Our superiority trial shows that 36 mo of ADT is not superior to 18 mo for the end point of death in localized HRPC. ADT combined with RT may potentially be reduced to 18 mo in selected men, which results in improved QoL on certain domains without compromising survival. ADT delivered for 18 mo seems to be an attractive alternative for patients not tolerating the ADT. Furthermore, ADT side effects and treatment costs can be significantly reduced with the shorter treatment duration. RT associated with 18 mo of ADT appears to represent a valid therapeutic option in localized HRPC.

Author contributions: Abdenour Nabid 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: Nabid.
Acquisition of data: Nabid, Martin, Bahoric, Lemaire, Vincent, Bahary, Souhami, Duclos, Bettahar, Archambault, Vass.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.05.020.

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