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THREE-MONTH DEPOT OF GOSERELIN ACETATE: CLINICAL EFFICACY AND ENDOCRINE PROFILE*

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ABSTRACT

Objectives. To compare the pharmacodynamics and tolerability of the new goserelin acetate 10.8-mg depot with the 3.6-mg depot in patients with advanced prostate cancer during the first 3 months of therapy.

Methods. One hundred sixty patients were randomized in two comparative studies to receive either the 10.8-mg goserelin acetate depot every 12 weeks or the 3.6-mg goserelin acetate depot every 4 weeks for 12 weeks and then the 10.8-mg depot every 12 weeks thereafter. Data for pharmacodynamic assessments were collected prospectively, whereas clinical response data were collected retrospectively.

Results. Serum testosterone profiles of the 10.8-mg goserelin acetate depot and the 3.6-mg goserelin acetate depot were similar; testosterone levels in both groups fell below castrate levels by day 21 after administration. Decreases in serum prostate-specific antigen level after 3 months of therapy were also similar in both groups: 94% with the 10.8-mg depot and 92.5% with the 3.6-mg depot. For all patients, the median time to progression was 152.7 weeks and the median time to death was 213.6 weeks. The safety profile of the 10.8-mg goserelin acetate depot was similar to that of the 3.6-mg depot; hot flashes was the most common adverse event. The incidence of injection site reactions was very low (2 [0.3%] of 614 administrations).

Conclusions. The new 10.8-mg depot was pharmacodynamically equivalent to the current 3.6-mg depot and was well tolerated, both locally and systemically. The observed times to progression and survival were as expected in this patient population. The 10.8-mg goserelin-acetate depot provided a dosing schedule that was convenient for the patient and the physician, and it has the potential to reduce health care costs while maintaining the quality of life in patients being treated for advanced prostate cancer. *Copyright 1996 by Elsevier Science Inc. UROLOGY 48: 894-900, 1996.*

Since their introduction over a decade ago as a treatment for advanced prostate cancer, luteinizing hormone-releasing hormone (LHRH) agonist analogues have displaced estrogens as the leading alternative to orchiectomy for patients undergoing monotherapy,¹ and they have emerged as a component of combination therapy with antiandrogens in patients receiving combined androgen

blockade.^{2,3} Because the commercially available depot formulations of LHRH analogues for prostate cancer require administration every 4 weeks, development of a convenient, longer-acting depot formulation has long been desired.

A new longer-acting, 3-month depot formulation of the LHRH analogue goserelin acetate implant (Zoladex, Zeneca Pharmaceuticals, Wilmington, Del, and Macclesfield, Cheshire, U.K.) was recently evaluated in clinical trials conducted in patients with advanced prostate cancer. In a Phase II study, effective suppression of serum concentrations of testosterone was achieved and maintained for at least 12 weeks following administration of the 10.8-mg depot formulation.⁴ In two Phase III studies,^{5,6} the pharmacodynamics, efficacy, and tolerability of the new 10.8-mg formulation were compared with the standard 3.6-mg

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formulation. Effective suppression of serum testosterone below the castrate level within 3 weeks and maintenance of suppression for the duration of therapy was achieved with both the 10.8- and 3.6-mg depot formulations. The 10.8-mg depot was well tolerated both locally and systemically.^{5,6} In this report, we update the pharmacodynamic and safety results of these two Phase III studies and present an analysis of prostate-specific antigen (PSA) response, time to progression, and survival.

MATERIAL AND METHODS

PATIENT SELECTION

Patients with histologic confirmation of prostate cancer, either locally advanced (T3, T4) or metastatic (M1) disease, with pretreatment serum testosterone within the normal range and a life expectancy of more than 6 months were eligible for entry. Patients previously treated with orchiectomy or hormonal treatment were excluded. All patients provided written informed consent, and the study was approved by the appropriate Institutional Review Boards.

STUDY DESIGN

The two multicenter, comparative studies (0001 and 1805) were of an identical, open, parallel-group design with a 48-week study period. Patients were randomized to one of two treatment groups: one group received the 10.8-mg depot formulation at 84-day intervals throughout the study; the other group initially received a subcutaneous injection of the 3.6-mg depot formulation of goserelin acetate, and, after three administrations at 28-day intervals, received subcutaneous injections of the 10.8-mg depot formulation at 84-day intervals throughout the remainder of the study.

TESTOSTERONE ASSESSMENTS

The primary objective of these studies was to compare the pharmacodynamics of the 10.8- and 3.6-mg goserelin acetate depots. The mean testosterone levels achieved during weeks 4 to 12 and at the end of weeks 4, 8, and 12 were compared between the 10.8- and the 3.6-mg treatment groups. In addition, the serum testosterone levels of individual patients were assessed according to secondary criteria for induction (defined as testosterone levels falling below the castrate level after the first administration) and maintenance (defined as serum testosterone levels remaining below the castrate level throughout a 12-week administration period).

Serum testosterone analyses were performed in a central laboratory, the Urological Research Laboratory (URL), at the University of Nijmegen, Nijmegen, The Netherlands. Total serum testosterone was assessed using a Diagnostic Products Corporation (DPC) radioimmunoassay kit (Los Angeles, Calif). This kit was previously tested against three other methods of testosterone measurement (a radioimmunoassay manufactured by Amersham, a fluorescence immunoassay manufactured by DELPHIA system [LKB-Pharmacia], and a paper chromatographic analysis [Endocrinology-KN]). These assays were compared using a series of testosterone levels from two sets of control sera (NMS I, II, and III and Lyphocheck [Biorad] I, II, and III). The results of the comparisons showed that, in the range of low testosterone levels, the variability with the DPC kit was lowest, approximately 20% (2.46 ± 0.46 nmol/L). Serum testosterone assay results from URL were also compared with results obtained from Endocrine Sciences Laboratory, Inc (ESL; Calabasas Hills, Calif [ESL used a column chromatographic assay]). The compar-

ison was made using samples obtained from 15 patients at the Nijmegen University Hospital who were being treated with LHRH analogues; these patients were not enrolled in the two studies that compared the 10.8- and 3.6-mg goserelin acetate depots.

In the current studies that compared the two depots, serum testosterone levels were measured before treatment, weekly for the first 4 weeks, then every 2 weeks until week 24, and then at weeks 36 and 48 (the day of administration of the first depot was defined as day 1). On days when sampling coincided with depot administration, samples were taken before administration of the depot. Serum testosterone was recorded as the mean value from duplicate assessments of the testosterone level of the sample. Internal quality-control samples (NMS and Lyphocheck) were included each time samples were assessed. When recorded results on any study day were greater than 2 nmol/L, the assessment was repeated and the new result was recorded as the testosterone value for that day, regardless of whether the new result was higher or lower than the original result. This castrate level was defined by using testosterone values in the castration range from 10 patients in a previous study with the goserelin acetate 10.8-mg depot. The mean testosterone value (0.95 nmol/L) obtained from these patients plus two standard deviations (two times 0.55 nmol/L) was used to arrive at the castrate level of 2.0 nmol/L.

EFFICACY EVALUATIONS

Data for PSA, time to progression, and survival were collected retrospectively by the Trialbureau Urology in Nijmegen and verified against hospital records. PSA results were compared between the 3.6- and 10.8-mg depots but only up until 3 months of therapy, because all patients received the 10.8-mg depot after that point. Results for time to progression and survival were combined for the two treatment groups to give an overview of disease outcome for these patients.

Changes in serum PSA alone were not considered evidence of disease progression. However, increases in PSA levels with subjective evidence of progression was considered evidence of progression.

Any one of the following was considered progression:

1. An increase greater than 50% in the value obtained when the largest diameter in one or more measurable lesions is multiplied by its longest perpendicular diameter
2. New soft-tissue metastasis
3. New osteolytic lesions or an increase of 25% or more in the size of existing osteolytic metastases
4. New "hot spots" on bone scintigraphy

For changes in PSA levels, stabilization was defined as an increase of greater than or equal to 50% of the baseline level confirmed by two assessments not less than 2 weeks apart. A PSA increase was defined as an increase greater than 4 ng/mL in patients who previously had a complete response, or an increase greater than 50% of the baseline level in patients who previously had a partial response, each confirmed by two assessments 2 weeks apart.

Any of the following was considered evidence of subjective progression:

1. Cancer-related decrease of greater than 25% of the hemoglobin measurement or the need for more than two blood transfusions a month
2. A cancer-related weight loss greater than 15%
3. A cancer-related increase in the performance-pain-analgesic-performance score

SAFETY EVALUATIONS

All patients who received study treatment were included in the safety evaluation. Adverse events were recorded at each

visit until patients completed their randomized therapy. Patients were solicited indirectly for adverse events; prompted by a question, each patient described anything that had bothered him since his last visit. In addition, any event considered by an investigator to be an adverse event was recorded.

STATISTICAL ANALYSIS

Mean testosterone level was the primary end point and was analyzed statistically between weeks 4 and 12 and at the end of weeks 4, 8, and 12. Analysis of variance (ANOVA) was used to compare mean testosterone levels between the 10.8-mg depot and the 3.6-mg depot for each of the two studies separately; the results were then pooled. One hundred fifty-six patients were analyzed using the intent-to-treat approach. Possible sources of variation of study, center within study, treatment, study by treatment interaction, and center by treatment interaction were taken into account.

Successful induction required at least one sample value being below the castrate level after the first depot. For successful maintenance, all patients receiving at least one depot were required to have no sample levels above the castrate level within 84 days of a depot administration, excluding the induction period for the first depot. A 95% confidence interval was derived for the difference in the percentage maintenance rates between the two treatment groups to assess the precision of this comparison.

The percent fall in PSA from the baseline value after 3 months of study treatment was calculated. The number and percentage of patients whose PSA values were elevated (greater than 4 ng/mL) at baseline and fell to within the normal range at month 3 were tabulated and compared between the two treatment groups.

Time to progression and time to death were estimated using the methods of Kaplan and Meier. Time to progression was defined as the number of days from the administration of the first goserelin acetate depot to the date of documentation of progression or death without progression. The time to death was defined as the number of days from the time of administration of the first goserelin acetate depot to the date of death from any cause. Data from patients who neither progressed nor died were censored at the time of their last visit to the clinic.

RESULTS

DEMOGRAPHY AND PATIENT CHARACTERISTICS

The age and body weight of patients from both treatment groups in both studies were similar at entry (Table I). Of the 80 patients entered into each study—between March 10, 1990, and July 8, 1992—67 (84%) patients in study 0001 and 66 (83%) patients in study 1805 were over 65 years of age.

TESTOSTERONE ASSESSMENTS

Mean testosterone levels between weeks 4 and 12 and at the end of weeks 4, 8, and 12 were below the castrate level; there were no significant differences between the 10.8- and 3.6-mg treatment groups (Table II).

Figure 1 illustrates the mean serum testosterone profile achieved in the two treatment groups. The profiles were similar for both groups, with testosterone levels falling below the castrate level by day 21 and then remaining below the castrate level un-

TABLE I. Demographic and pretreatment characteristics

	Treatment Group	
	3.6-mg Depot (n = 83)	10.8-mg Depot (n = 77)
Age (yr)		
Mean	72	73
Range	52–89	49–88
Weight (kg)		
Mean	76	77
Range	48–108	53–105
Stage (TMN classification)		
T0	0	2
T1	0	2
T2	7	21
T3	46	38
T4	26	11
Tx	4	3
M0	28	25
M1	43	44
Mx	12	8
G1	15	9
G2	38	38
G3	26	26
Gx	4	4

TABLE II. Testosterone level suppression (nmol/L)*

Weeks of Treatment	Treatment Group	
	3.6-mg Depot (n = 83)	10.8-mg Depot (n = 77)
Week 0	17.91 ± 6.99 (n = 75)	18.48 ± 6.35 (n = 75)
Week 4	1.05 ± 2.04 (n = 76)	0.92 ± 0.47 (n = 73)
Week 8	0.60 ± 0.39 (n = 70)	0.62 ± 0.49 (n = 70)
Week 12	0.60 ± 0.36 (n = 65)	0.73 ± 0.69 (n = 69)

* Mean ± standard deviation.

til week 12. Beyond week 12, when both groups were receiving the 10.8-mg depot, levels achieved in both groups were maintained below the castrate level.

Adequate suppression of testosterone was maintained in 99.4% of the patients. Only 1 (0.6%) patient did not have adequate suppression during therapy; this patient received the 10.8-mg depot. In 8 other patients, a transient elevation in testosterone levels above the castrate level was followed by a return within 14 days to levels within the castrate range. The clinical outcome for these pa-

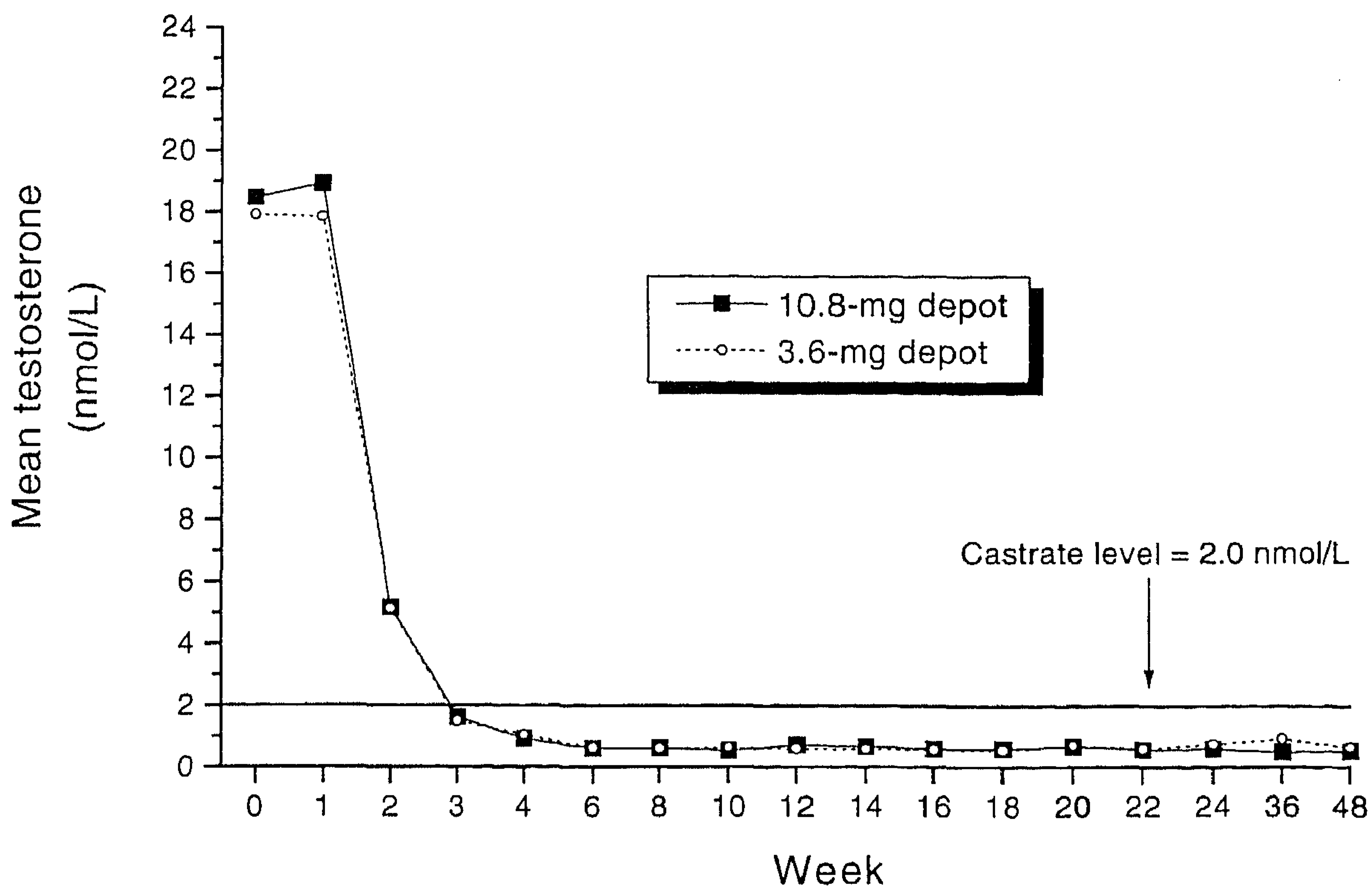


FIGURE 1. Mean serum testosterone levels over 48 weeks. (Reprinted with permission from Debruyne FM, Dijkman GA, Lee DCH, and Witjes WPJ, on behalf of the Dutch South East Cooperative Urological Group: A new long-acting formulation of the luteinizing hormone-releasing hormone analogue, goserelin: results of studies in prostate cancer. *J Urol* 155: 1352-1354, 1996.)

tients was similar to that observed for the rest of the patients in these studies.

Figure 2 shows the results of the comparison of assay results from URL and ESL. URL reported higher testosterone levels for all samples, indicating a clear difference between the two testosterone assays.

EFFICACY

PSA results were available at baseline and at 12 weeks for 54 of the 83 patients in the 3.6-mg group and 54 of the 77 patients in the 10.8-mg group. The percentages of patients with PSA values that fell to within the normal range following 3 months of study treatment were similar between treatments: 26 (48%) of 54 patients treated with the 3.6-mg depot and 28 (52%) of 54 patients treated with the 10.8-mg depot. The median percentage fall in serum PSA was also similar in both groups: 92.5% for those treated with the 3.6-mg depot and 94.0% for those treated with the 10.8-mg depot.

One hundred five (66%) of the 160 patients had progressed at the time of this analysis. The median time to progression was 152.7 weeks. The Kaplan-Meier probability of progression is presented in Figure 3.

Eighty-three (52%) of the 160 patients had died at the time of this analysis. Fifty-three (64%) of

the 83 patients who had died did so as a result of prostate cancer alone, 25 (30%) died as a result of other causes, and 5 (6%) died as a result of unknown causes; the observed causes of death were not unexpected in this patient population, and none of the deaths were attributed to treatment. The median time to death was 213.6 weeks. The Kaplan-Meier probability of death is presented in Figure 4.

SAFETY

During the comparative phase (weeks 0 through 12), the only adverse event reported in more than 5% of patients was hot flashes, with an incidence of 47% in the 10.8-mg group and 48% in the 3.6-mg group. Adverse events occurring in more than 5% of patients during the noncomparative phase (weeks 12 through 48) are presented in Table III. Only 1 patient had an adverse event that led to withdrawal; the patient had mild pruritus from paraneoplastic dermatitis while he was receiving the 10.8-mg depot preparation of goserelin. The adverse event was considered unrelated to therapy with 10.8-mg goserelin. Tumor flare was reported in 6 patients, including 4 in the 3.6-mg treatment group and 2 in the 10.8-mg treatment group. One patient in each group had a spinal cord compression: 1 patient had medullary compression 8 days

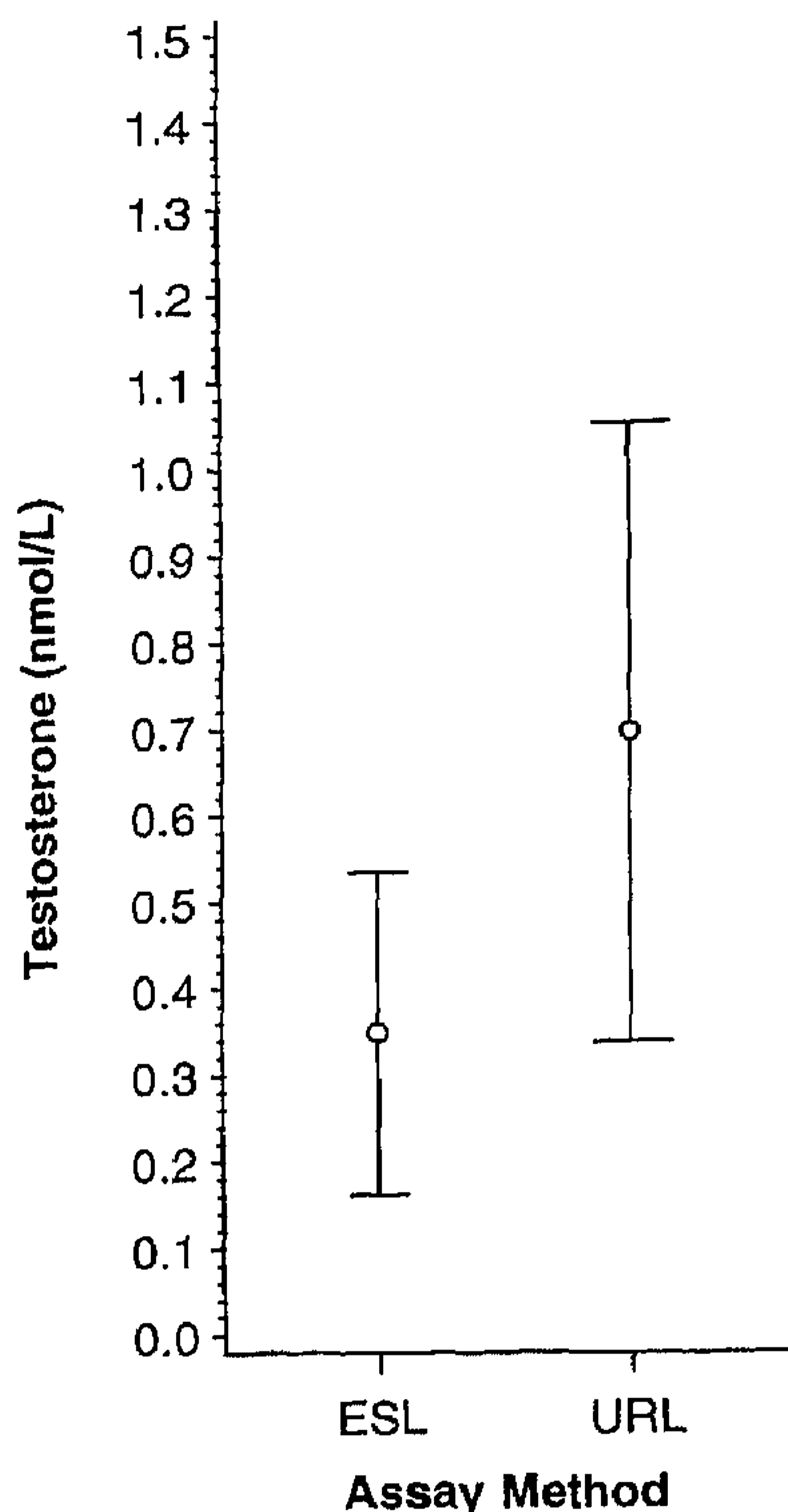


FIGURE 2. Comparison of serum testosterone levels reported by the Urological Research Laboratory (URL) and Endocrine Sciences Laboratory (ESL).

after receiving the first goserelin 3.6-mg depot; another patient had spinal cord compression on the same day as the first administration of the 10.8-mg goserelin depot. Both events were considered by the investigator to be related to disease progression. Only 2 (0.3%) of 614 administrations of the 10.8-mg depot resulted in local reactions; both

were hematomas and did not require specific management. A local anesthetic was not required on 597 (97%) occasions out of 614 administrations of the 10.8-mg depot.

COMMENT

The combined results from the two studies, which include data from a total of 160 patients, demonstrate that the 10.8-mg depot formulation of goserelin acetate is pharmacodynamically equivalent to three consecutive administrations of the 3.6-mg depot, with regard to induction and maintenance of serum testosterone suppression. Adequate suppression of serum testosterone was maintained in 99.4% of the patients. During treatment, 9 patients had at least one serum testosterone value above the castrate level of 2.0 nmol/L, eight of which were transient and isolated; however, the clinical outcome of these patients, as measured by time to progression and survival, was no different from that of the rest of the patients in these studies. Only 1 patient was considered to have failed initial treatment with goserelin acetate for part of the treatment period; the resultant failure rate of 0.6% (1 of 160) was considered acceptable. Ultimately, with the continued administration of goserelin acetate during the follow-up period, this patient's serum testosterone level was adequately suppressed and the clinical course of his disease was considered by the investigator not to have been adversely affected.

The difference in results between the URL and ESL testosterone assays underline the importance of defining the castrate level using the local patient

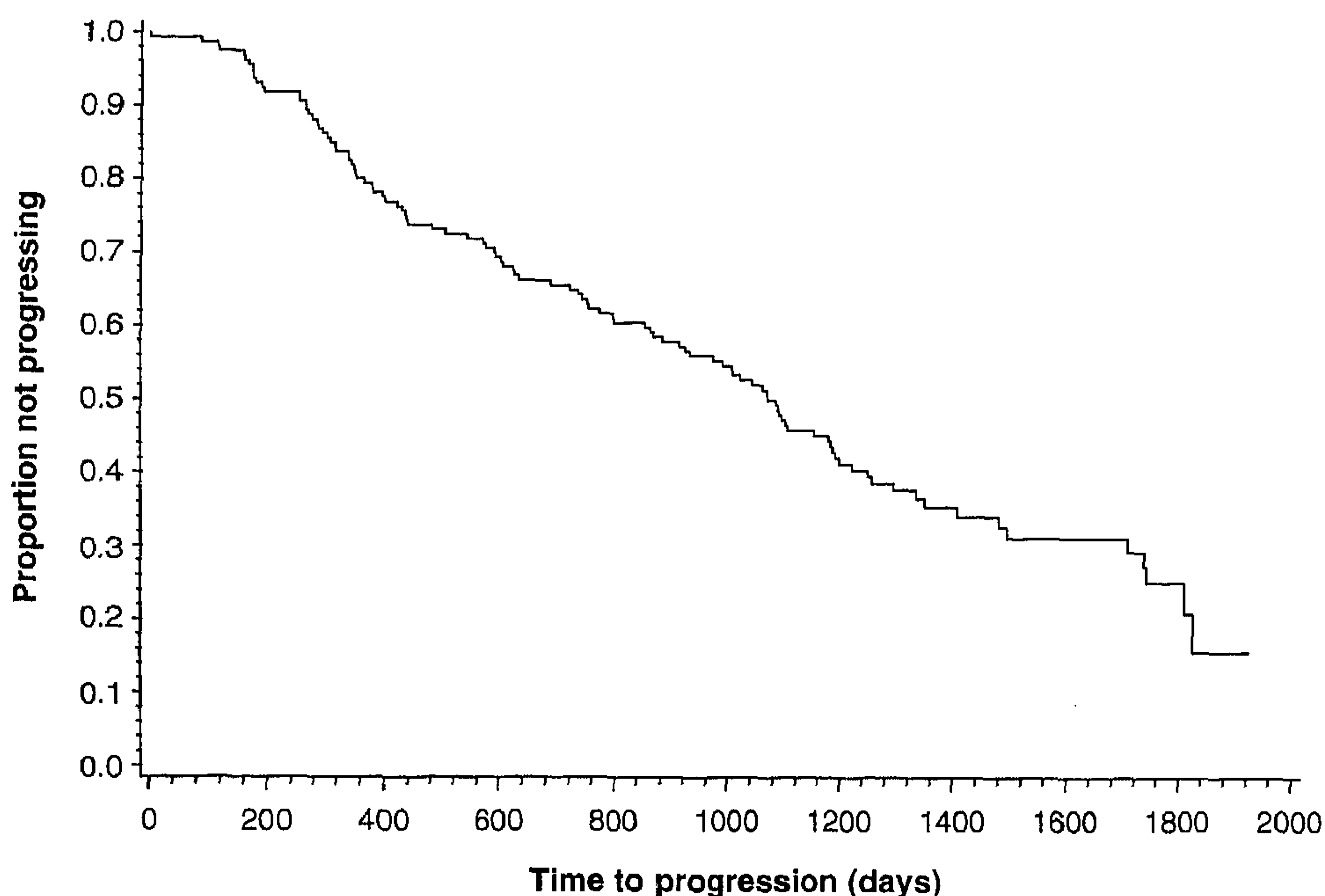


FIGURE 3. Kaplan-Meier probability of progression.

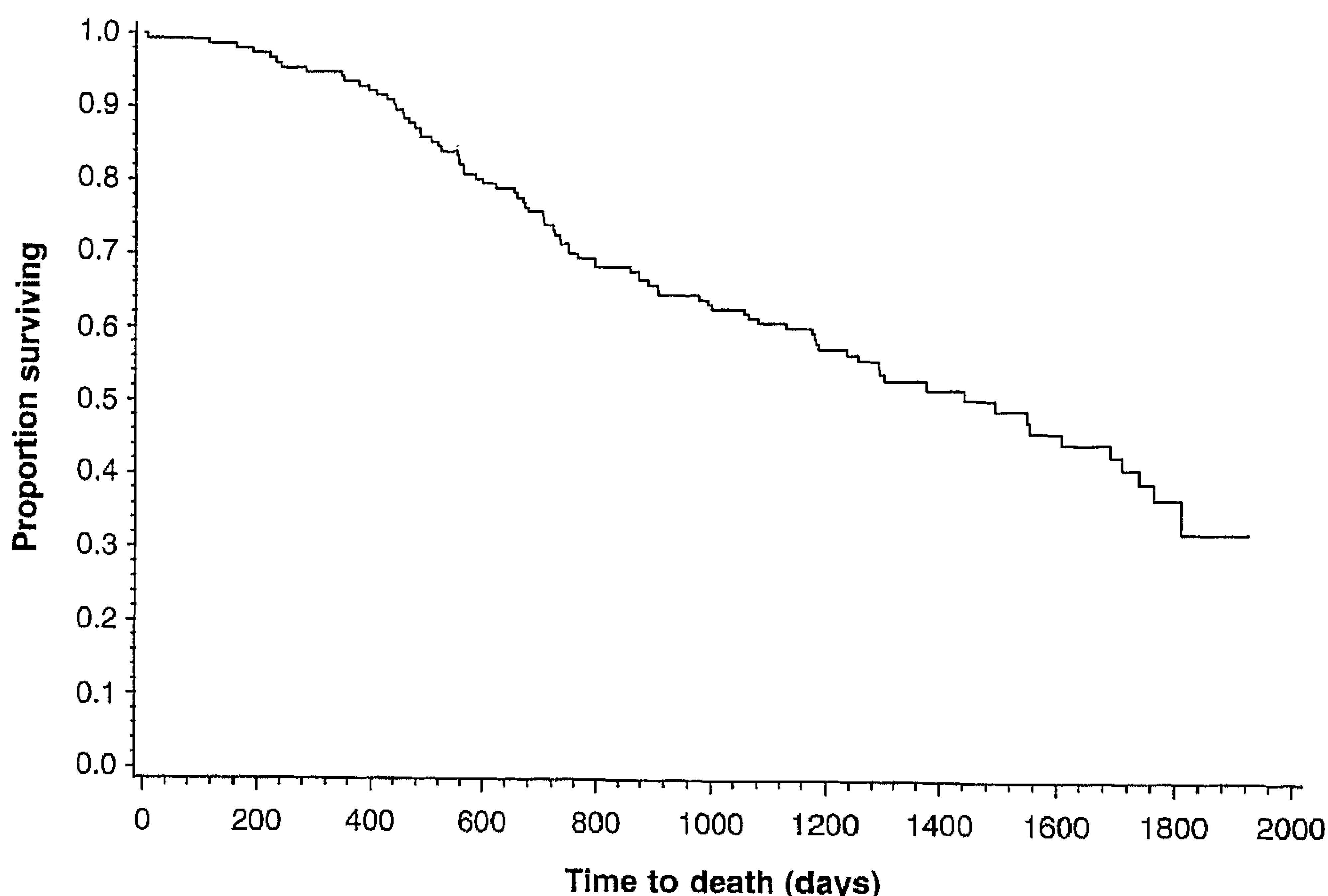


FIGURE 4. Kaplan-Meier probability of death.

TABLE III. Adverse events reported in more than 5% of patients during the noncomparative phase, weeks 12 to 48 (n = 157)

Adverse Event	10.8-mg Depot
Hot flashes	100 (64%)
Pain	22 (14%)
Gynecomastia	13 (8%)
Pelvic pain	10 (6%)
Bone pain	9 (6%)

population and assay. It also suggests that choosing a different castrate level (for example, from literature references) may lead to different conclusions, depending on the actual assay used.

The median time to progression (152.7 weeks) and median survival time (213.6 weeks) with the 10.8-mg depot were longer than those previously reported with the 3.6-mg depot. Kaisary *et al.*⁷ reported a median time to treatment failure of 26.9 weeks and a median survival time of 110 weeks, whereas Vogelzang *et al.*⁸ reported median times to treatment failure and survival of 52 and 119 weeks, respectively; both used the 3.6-mg depot. The differences between the previously published reports and the current studies may be due to different patient populations; whereas the previous reports mainly studied patients with metastatic prostate cancer, the current studies included patients with both locally advanced and metastatic disease.

The adverse event profile of the 10.8-mg goserelin depot was similar to that of the 3.6-mg depot.

The 10.8-mg depot was well tolerated, and the incidence of injection site reactions was low (0.3%). Tumor flare was reported in 6 patients (4 in the 3.6-mg group and 2 in the 10.8-mg group), but none of the patients withdrew because of this adverse event. It is possible that coadministration of antiandrogen therapy with LHRH-A therapy could have prevented or lessened the severity of tumor flare in these patients.

The 10.8-mg goserelin-acetate depot is an acceptable and effective method for suppressing serum testosterone levels, providing a dosing schedule that is convenient for the patient and the physician and that coincides with the routine care of patients with advanced prostate cancer. The 10.8-mg depot also has the potential to reduce health care costs by reducing the number of health care provider contacts, while maintaining the quality of life of patients being treated for advanced prostate cancer.

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APPENDIX

Additional members of the Dutch South East Cooperative Group who participated in these studies are Dr. A.P.M. van der Meijden, Ziekengasthuis, 'S Hertogenbosch; Dr. J.W.M.H. Plasman, St. Franciscus Ziekenhuis, Roosendaal; Dr. H.C. Pull, St. Ziekenhuis Lievensberg, Bergen Op Zoom; Dr. J.J. Kums, St. Sophia Hospital, Zwolle; Dr. J.G. Idema, Ziekenhuis Rijnstate, Arnhem; Dr. J.W. Hoefakker, Ziekenhuis Rijnstate, Arnhem; Dr. H.F.M. Karthaus, Canisius Wilhelmina Ziekenhuis, Nijmegen; Dr. R.P. Heijbroek, Vereniging Het Ziekenhuis Velp, Velp; Dr. P.J.M. Kil, St. Elisabeth Ziekenhuis, Tilburg; and Dr. G.S.S. Khoe, Medisch Spectrum Twente, Enschede.