ORIGINAL ARTICLE

Transdermal Estradiol Patches in Locally Advanced Prostate Cancer

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ABSTRACT

BACKGROUND

Transdermal estradiol (tE2) is an alternative to luteinizing hormone–releasing hormone (LHRH) agonists as androgen-deprivation therapy in patients with prostate cancer. With tE2, testosterone is suppressed, and the side effects of estrogen depletion due to LHRH agonists and the thromboembolic side effects of oral estrogen are mitigated.

METHODS

In this phase 3, noninferiority, randomized trial, we assigned men with locally advanced (M0 and N0 or N+) prostate cancer to receive tE2 patches (100 μg of estradiol every 24 hours) or LHRH agonists. The primary outcome was 3-year metastasis-free survival. The noninferiority margin was 4 percentage points; this corresponded to a target hazard ratio of 1.31, as derived from the observed 3-year metastasis-free survival in the LHRH agonist group. Secondary outcomes included castrate levels of testosterone (<1.7 nmol per liter), overall survival, and safety.

RESULTS

Between 2007 and 2022, we recruited 1360 patients at 75 U.K. centers. The median age of the patients was 72 years (interquartile range, 68 to 77); 85% had a T3 tumor stage and 65% an N0 nodal stage. Observed 3-year metastasis-free survival was 87.1% with tE2 and 85.9% with LHRH agonists (hazard ratio for confirmed metastasis or death, 0.96; upper limit of the one-sided 95% confidence interval [CI], 1.11, which met the criterion for noninferiority). Among patients continuing the assigned treatment, castrate levels of testosterone were sustained during the first year after randomization in 85% in each group. Observed 5-year overall survival was 81.1% with tE2 and 79.2% with LHRH agonists (hazard ratio for death, 0.90; 95% CI, 0.75 to 1.07). During treatment, hot flashes occurred in 44% of the patients who received tE2 and 89% of those who received LHRH agonists (grade ≥2 events, 8% and 37%, respectively) and gynecomastia in 85% and 42% (grade ≥2 events, 37% and 9%).

CONCLUSIONS

In patients with locally advanced prostate cancer, tE2 was noninferior to LHRH agonists for 3-year metastasis-free survival, with a lower incidence of hot flashes but a higher incidence of gynecomastia. (Funded by Cancer Research U.K. and the U.K. Research Institute Medical Research Council; PATCH ClinicalTrials.gov number, NCT00303784; STAMPEDE-1 ClinicalTrials.gov number, NCT00268476.)

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Prostate cancer is the most common cancer worldwide among men.[1] Reducing serum testosterone levels to less than 1.7 nmol per liter (<50 ng per deciliter), often referred to as castrate levels of testosterone, is the backbone of therapy for locally advanced nonmetastatic (metastasis stage M0) and metastatic (stage M1) disease.[2] This reduction is most commonly achieved with luteinizing hormone–releasing hormone (LHRH) agonists, which also reduce serum estradiol levels given that approximately 80% of estrogens in men are derived from the aromatization of testosterone.[3] LHRH agonists have several toxic effects, including erectile dysfunction and loss of muscle mass due to decreased testosterone levels and loss of bone mineral density (which increases the risk of osteoporosis and fracture), adverse metabolic changes (increased levels of serum lipids and glucose and increased blood pressure), and hot flashes due to decreased estradiol levels.[4-6]

The administration of exogenous estrogen is an alternative approach to treatment that lowers testosterone levels by means of a negative feedback loop involving the hypothalamus and pituitary gland but mitigates the effects of estrogen depletion.[7] This approach was first investigated with oral estrogen (stilbestrol), which lowered testosterone levels and improved prostate cancer outcomes but was associated with an increased incidence of thromboembolic events[8] attributed to first-pass hepatic metabolism and increased levels of liver-derived plasma proteins and coagulation factors.[9] Estrogen administered parenterally by means of a transdermal patch avoids first-pass hepatic metabolism and therefore carries a lower risk of cardiovascular thromboembolic complications than orally administered estrogen.[10]

We conducted a phase 2–3 adaptive trial to assess the safety and efficacy of transdermal estradiol (tE2) patches in patients with prostate cancer who were recruited through the PATCH (Prostate Adenocarcinoma Transcutaneous Hormones) or STAMPEDE-1 (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial networks. We initially performed a phase 2 randomized trial that compared tE2 patches with LHRH agonists with respect to the primary outcome of cardiovascular morbidity and mortality in 200 patients with locally advanced and metastatic prostate cancer.[11] The trial showed a better metabolic profile and no early evidence of higher cardiovascular risk with tE2. Results of additional assessments confirmed the preservation of bone mineral density and improved quality-of-life scores with tE2 patches as compared with LHRH agonists.[12,13] The recruitment period was then extended, and in a cohort of 1694 men, we confirmed no excess cardiovascular toxic effects with longer follow-up.[10] Next, we expanded the program into two separate phase 3 trials to compare the efficacy of tE2 patches with that of LHRH agonists in patients with metastasis stage M0 prostate cancer or metastasis stage M1 prostate cancer. Here, we report results from the phase 3 trial involving patients with metastasis stage M0 disease.

Methods

Trial Design and Oversight

This trial was an academically led, phase 2–3, seamless, adaptive, randomized trial that was embedded within a broader program to evaluate tE2 in prostate cancer (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[14] Patients were recruited at sites in the PATCH trial network; from 2017 onward, patients were also recruited at sites in the STAMPEDE-1 trial network. STAMPEDE-1 is an established trial with an adaptive, multigroup, multistage (also known as multiarm, multistage [MAMS]) design that permits the addition of new trial questions.[15]

The trial was sponsored by Imperial College London initially and by University College London from 2020 onward. The U.K. Medical Research Council Clinical Trials Unit at University College London conducted the trial. Funding throughout the trial was provided by the U.K. Medical Research Council. Cancer Research U.K. approved the trial design and provided funding for the collection and analysis of the data. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonisation and was approved by the appropriate regulatory authorities and ethics committees. The decision to submit the manuscript for publication was made by the PATCH and STAMPEDE-1 trial management groups. The au-

thors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

PATIENTS

Patients with histologically confirmed, localized adenocarcinoma of the prostate who were scheduled to start androgen-deprivation therapy and had a World Health Organization (WHO) performance-status score of 2 or lower (range, 0 to 5, with higher scores reflecting greater disability) were eligible for the trial. Additional eligibility criteria included a tumor stage of T3 or T4, with a nodal stage of N0 or NX and a metastasis stage of M0, as assessed with contemporary imaging (bone scan or chest radiography initially and computed tomography or magnetic resonance imaging subsequently), plus a prostate-specific antigen (PSA) level of at least 20 ng per milliliter or a Gleason sum of at least 6 (range, 2 to 10; sums of ≤6 indicate lower-grade prostate cancer, and higher sums indicate more aggressive cancer); or any tumor stage with a nodal stage of N+ and a metastasis stage of M0, irrespective of the PSA level or Gleason sum. Patients with a relapse after radical local radiotherapy were also eligible if they had a PSA level of at least 4 ng per milliliter with a doubling time of less than 6 months, a PSA level of at least 20 ng per milliliter, or a tumor with an N+ nodal stage.

Patients who had a clinically significant history of cardiovascular disease as previously described[10] and those who were considered to be unfit for the trial therapies were excluded. Eligibility criteria as defined in the PATCH and STAMPEDE-1 protocols were closely aligned.

TRIAL PROCEDURES

Patients were randomly assigned to receive tE2 patches or LHRH agonists according to local practice without blinding. Randomization was conducted with a computer-based minimization algorithm with a random element of 20%. The first 200 patients — all of whom were enrolled at a PATCH site — were assigned in a 2:1 ratio to receive tE2 patches or LHRH agonists; this ratio was used to increase the number of patients early during the trial who had experience using the patches. Subsequent patients were assigned in a 1:1 ratio to the two treatment groups. Stratification factors common to PATCH and STAMPEDE-1 included age, disease status, specific LHRH agonist used, and treating physician's intention to perform radical prostate radiotherapy, provide adjuvant docetaxel, or both. Additional stratification factors included smoking status, history of cardiac disease in a first-degree relative, trial center, and PSA level at trial entry in PATCH and WHO performance-status score and use of nonsteroidal antiinflammatory drugs in STAMPEDE-1.

LHRH agonists were injected subcutaneously every 4 or 12 weeks; treatment with bicalutamide or flutamide for up to 8 weeks was permitted to prevent a temporary increase in the PSA level or symptoms. The tE2 patches (Progynova or FemSeven), which released 100 μg of estradiol per 24 hours, were applied by the patient. The initial dose was four patches twice weekly. If a serum castrate level of testosterone (<1.7 nmol per liter) was present at 4 weeks, the dose was reduced to three patches twice weekly. Levels of estradiol, testosterone, and PSA were monitored at 4, 12, and 26 weeks and every 6 months thereafter. The target range of the estradiol level was 250 to 2000 pmol per liter. Evolving standards of care that were incorporated into the protocol included radiotherapy to the prostate (added in January 2014),[16] concomitant docetaxel therapy for up to six cycles (added in October 2015),[17] and decreasing the duration of androgen-deprivation therapy to a minimum of 2 years.[18] Prophylactic irradiation of the breast area (given in a single fraction of 8 Gy) was permitted to prevent gynecomastia. Use of tamoxifen to prevent gynecomastia was not permitted because it is an antiestrogen agent. Patient management at the time of disease progression was at the discretion of the treating physician and included crossover to the alternate androgen-deprivation therapy and the addition of additional therapies.

OUTCOMES

The primary outcome was 3-year metastasis-free survival, with survival calculated as the time from randomization to confirmation of metastasis (excluding pelvic lymph node progression) or death from any cause. Metastasis-free survival is a recognized surrogate for overall survival.[19] Secondary outcomes included castrate levels of testosterone, overall survival, and safety.

STATISTICAL ANALYSIS

We estimated that 510 primary-outcome events would provide the trial with 85% power to rule out an absolute difference of more than 4 percentage points in 3-year metastasis-free survival between the treatment groups, at a one-sided significance level of 5%. This estimate assumed a 3-year metastasis-free survival of 83% in the LHRH agonist group, corresponding to a hazard ratio for confirmed metastasis or death from any cause of 1.27.

Data for this analysis were frozen in the database on February 27, 2025. Follow-up was considered to be up to date if the patient had a confirmed date of death, had a confirmed date of withdrawal from the trial or loss to follow-up, or was alive and had a follow-up visit after January 2023. The primary outcome was analyzed with a fixed-effects model according to an approach similar to that of a meta-analysis. Patients recruited at PATCH sites and assigned to receive tE2 or LHRH agonists at a ratio of 2:1, those recruited at PATCH sites and assigned at a ratio of 1:1, and those recruited at STAMPEDE-1 sites were considered to be three separate cohorts. Cox models were used to generate hazard ratios, which included terms for age (<70 or ≥70 years), baseline PSA level (<50, 50 to <500, or ≥500 ng per milliliter), nodal stage (N0, N+, or Nx), WHO performance-status score (0, 1, or 2), past use of LHRH agonists (yes or no), and treating physician's intention to provide radiotherapy (yes or no) and docetaxel therapy (yes or no).

Pooled data across the three cohorts showed an observed 3-year metastasis-free survival of 85.9% in the LHRH agonist groups. To maintain the noninferiority margin of 4 percentage points, the upper limit of the one-sided 95% confidence interval of the hazard ratio for confirmed metastasis or death from any cause would need to be less than the target hazard ratio of 1.31 derived on the basis of pooled data from the LHRH agonist groups, under the assumption of proportional hazards and an exponential survival distribution. Unless otherwise specified, all analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. Secondary analyses were not adjusted for multiple testing, and the confidence intervals should not be used to infer definitive treatment effects.

Patients in PATCH were included in the analyses of castrate levels of testosterone if they were receiving the assigned treatment and had data on the testosterone level at baseline, month 1 (window, ±1 week) and months 3, 6, and 12 (window, ±4 weeks). Patients in STAMPEDE-1 were not included in these assessments because testosterone levels were not recorded at baseline or in the LHRH agonist group during the treatment period. The percentage of patients with sustained castrate levels of testosterone during the first year of treatment was assessed in a time-to-event analysis as previously described[20]; testosterone levels that were measured within 35 days after the start of treatment were excluded from the analysis to account for the initial increase that may occur with LHRH agonists. Data for patients who stopped the assigned treatment before a castrate level of testosterone was detected were censored on the date of the last testosterone test during treatment. Patients were considered to have stopped the assigned treatment at the time of withdrawal or death or if treatment cessation was confirmed during a follow-up visit. Data for patients in the tE2 group with a serum estradiol level of 250 pmol per liter or less during a trial visit were censored at that time point because they were considered to have been nonadherent to the patch regimen.

The safety analysis included all the patients with data collected on adverse events during at least one follow-up visit. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Data on fractures were limited to patients in PATCH; these data were obtained from forms that were used to record data on toxic effects and serious adverse events and were analyzed by means of competing-risk survival methods with death as a competing risk.

RESULTS

PATIENTS

We recruited 1082 of 1360 patients (80%) at 75 sites in the PATCH trial network between 2007 and 2022 and 278 patients (20%) at sites in the STAMPEDE-1 trial network from 2017 onward. Overall, 721 patients (53%) were assigned to receive tE2 and 639 (47%) to receive LHRH agonists; these assignments reflect the shift from the randomization ratio of 2:1 to the ratio of 1:1 in PATCH (Fig. 1). Only 35 patients (3%) did not

have follow-up data that met prespecified criteria to be considered up to date.

Baseline characteristics were balanced between the treatment groups (Table 1). The median age was 72 years (interquartile range, 68 to 77), and 897 patients (66%) were 70 years of age or older. A total of 1032 patients (76%) had a WHO performance-status score of 0. The median PSA level at trial entry was 24.4 ng per milliliter (interquartile range, 11.8 to 54.1), and 810 patients (60%) had a Gleason sum of 8, 9, or 10. Overall, 1157 patients (85%) had a tumor stage of T3, and 883 (65%) had a nodal stage of N0. Radiotherapy to the prostate was planned by the treating physician for 928 patients (68%), and concomitant use of docetaxel was planned for 80 (6%); both treatments were added to the protocol as standard care during the recruitment period.

Baseline characteristics in PATCH and STAMPEDE-1 were generally similar, as were those in the 2:1 randomization cohort (144 of 1360 patients; 11%) and 1:1 randomization cohort (1216 patients; 89%) in PATCH (Table S1). The median age among the 144 patients in the 2:1 randomization cohort was higher than that among those in the 1:1 randomization cohort and among those in STAMPEDE-1, with 110 (76%) having an age of at least 70 years and 91 (63%) having a WHO performance-status score of 0. The median age among the 278 patients in STAMPEDE-1 was lower than that among those in the PATCH randomization cohorts, with 152 (55%) having an age of at least 70 years; 242 (87%) having a WHO performance-status score of 0; 220 (79%) having a Gleason sum of 8, 9, or 10; and radiotherapy to the prostate was planned by the treating physician for 257 (92%). The higher percentage of patients in STAMPEDE-1 who had radiotherapy planned was a reflection of the more recent recruitment period in this trial.

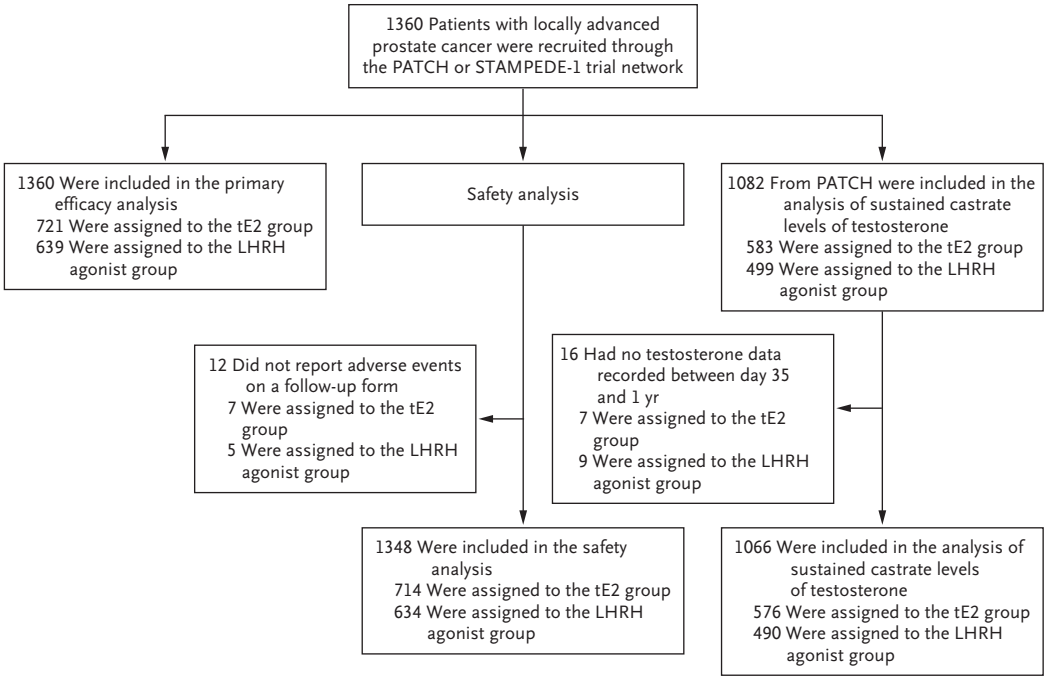


Figure 1. Randomization and Follow-up of the Patients.

Patients who were continuing the assigned treatment were included in the analysis of sustained castrate levels of testosterone (<1.7 nmol per liter [<50 ng per deciliter]). Adherence to transdermal estradiol (tE2) therapy was defined by an estradiol level of more than 250 pmol per liter. Patients in STAMPEDE-1 were not included in the assessment of castrate levels of testosterone because testosterone levels were not recorded at baseline or in the LHRH agonist group during the treatment period. PATCH denotes Prostate Adenocarcinoma Transcutaneous Hormones, and STAMPEDE-1 Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	tE2 (N=721)	LHRH Agonists (N=639)	Total (N=1360)
Trial — no. (%)			
PATCH	583 (81)	499 (78)	1082 (80)
STAMPEDE-1	138 (19)	140 (22)	278 (20)
Age			
Median (IQR) — yr	72 (68–77)	72 (67–77)	72 (68–77)
Range — yr	46–90	50–89	46–90
Distribution — no. (%)			
<70 yr	244 (34)	219 (34)	463 (34)
≥70 yr	477 (66)	420 (66)	897 (66)
WHO performance-status score — no. (%)†			
0	544 (75)	488 (76)	1032 (76)
1	154 (21)	139 (22)	293 (22)
2	23 (3)	12 (2)	35 (3)
Tumor stage — no. (%)			
T0	0	1 (<1)	1 (<1)
T1	5 (1)	5 (1)	10 (1)
T2	25 (3)	21 (3)	46 (3)
T3	615 (85)	542 (85)	1157 (85)
T4	72 (10)	67 (10)	139 (10)
TX	4 (1)	2 (<1)	6 (<1)
Nodal stage — no. (%)			
N0	456 (63)	427 (67)	883 (65)
N+	164 (23)	150 (23)	314 (23)
NX	101 (14)	62 (10)	163 (12)
Prostate-specific antigen level			
Median (IQR) — ng/ml	25.21 (12–54.9)	23.8 (11.3–53.1)	24.4 (11.8–54.1)
Range — ng/ml	0.8–544.1	1.1–2488.0	0.8–2488.0
Distribution — no. (%)			
<50 ng/ml	519 (72)	474 (74)	993 (73)
50 to <500 ng/ml	201 (28)	161 (25)	362 (27)
≥500 ng/ml	1 (<1)	4 (1)	5 (<1)
Gleason sum, ungrouped — no. (%)‡			
4	0	1 (<1)	1 (<1)
5	3 (<1)	5 (1)	8 (1)
6	35 (5)	33 (5)	68 (5)
7	253 (35)	213 (33)	466 (34)
8	158 (22)	139 (22)	297 (22)
9	253 (35)	238 (37)	491 (36)
10	13 (2)	10 (2)	23 (2)

Table 1. (Continued)

Characteristic	tE2 (N=721)	LHRH Agonists (N=639)	Total (N=1360)
Gleason sum, grouped — no. (%)‡			
4, 5, or 6	39 (5)	39 (6)	77 (6)
7	253 (35)	213 (33)	466 (34)
8, 9, or 10	424 (59)	387 (61)	811 (60)
Standard care planned by treating physician — no. (%)§			
Radiotherapy to prostate			
No	241 (33)	191 (30)	432 (32)
Yes	480 (67)	448 (70)	928 (68)
Docetaxel or abiraterone			
No	683 (95)	596 (93)	1279 (94)
Docetaxel	37 (5)	43 (7)	80 (6)
Abiraterone	1 (<1)	0	1 (<1)

* Percentages may not sum to 100 because of rounding. IQR denotes interquartile range, LHRH luteinizing hormone–releasing hormone, PATCH Prostate Adenocarcinoma Transcutaneous Hormones, STAMPEDE-1 Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy, and tE2 transdermal estradiol.

† Patients with a World Health Organization (WHO) performance-status score of 2 or lower were eligible for the trial. Scores range from 0 to 5, with a score of 0 indicating normal activity without restriction; 1 strenuous activity restricted, can do light work; 2 up and about more than 50% of waking hours, limited self-care; and 3 or higher greater disability.

‡ The Gleason sum is a measure of the aggressiveness of prostate cancer. Sums range from 2 to 10, with a sum of 6 or lower indicating lower-grade prostate cancer and higher sums indicating more aggressive cancer.

§ Radiotherapy to the prostate as standard care was added to the protocol in January 2014,[16] and concomitant docetaxel therapy for up to six cycles as standard care was added in October 2015.

PRIMARY OUTCOME

At the time of the primary analysis, confirmed metastasis or death from any cause had occurred in 568 patients. The observed 3-year metastasis-free survival was 87.1% in the tE2 group and 85.9% in the LHRH agonist group (difference, 1.2 percentage points; 95% confidence interval [CI], –2.5 to 4.9). The hazard ratio for confirmed metastasis or death from any cause was 0.96 (upper limit of one-sided 95% CI, 1.11; two-sided 95% CI, 0.81 to 1.14) (Fig. 2A). The upper limit of the one-sided 95% confidence interval for the hazard ratio was less than the target hazard ratio of 1.31 derived on the basis of pooled data from the LHRH agonist groups and was equivalent to excluding a between-group difference of 2 percentage points in metastasis-free survival. These findings show that tE2 was noninferior to LHRH agonists for 3-year metastasis-free survival.

ADDITIONAL OUTCOMES

Metastasis-free survival according to trial cohort, PATCH randomization ratio, and treating physician's intention to provide radiotherapy is shown along with confidence intervals in Figure S2A and S2B. The observed 5-year overall survival was 81.1% in the tE2 group and 79.2% in the LHRH agonist group (difference, 1.8 percentage points; 95% confidence interval, –2.6 to 6.2), with a hazard ratio for death of 0.90 (95% CI, 0.75 to 1.07) (Fig. 2B). The observed overall survival in the two PATCH randomization cohorts and STAMPEDE-1 is shown in Figure S2C. Causes of death are shown in Table S2. Death occurred in 501 patients (37%), of whom 213 (43%) died from prostate cancer. Other important causes of death included a second primary cancer (in 65 patients; 13% of deaths), cardiovascular disease (in 60; 12%), and respiratory disease, including bronchopneumonia (in 79; 16%). Causes of

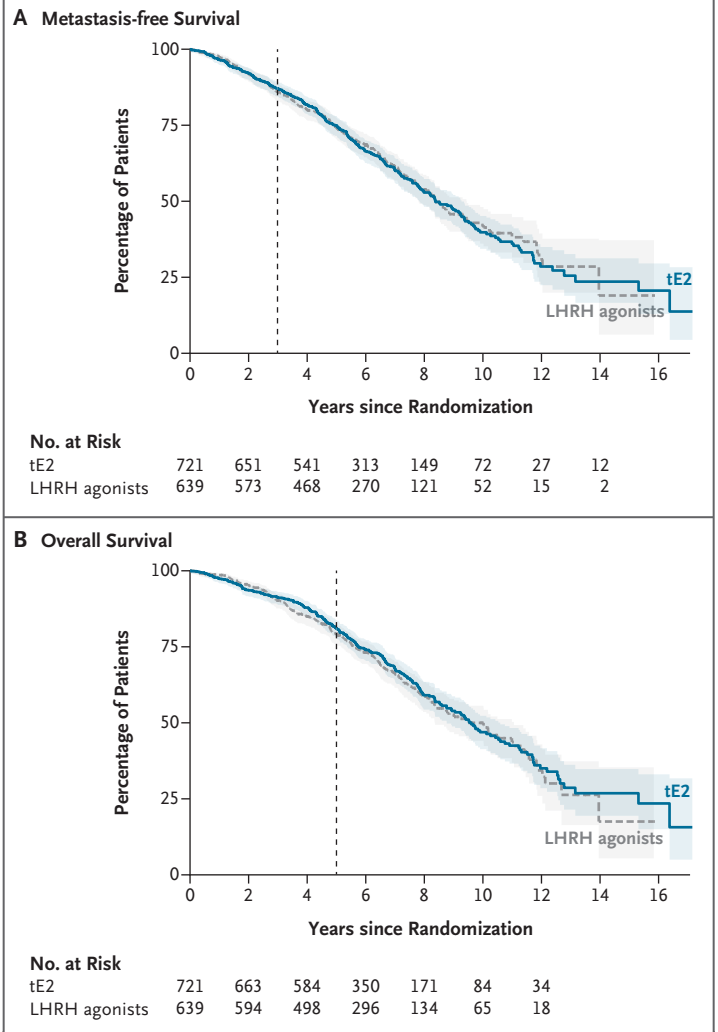


Figure 2. Metastasis-free Survival and Overall Survival.

The observed 3-year metastasis-free survival was 87.1% with tE2 and 85.9% with LHRH agonists, with a hazard ratio for confirmed metastasis or death from any cause of 0.96 (upper limit of one-sided 95% confidence interval [CI], 1.11) (Panel A). The upper limit of the one-sided 95% confidence interval was less than the target hazard ratio of 1.31 derived on the basis of pooled data from the LHRH agonist groups in PATCH and STAMPEDE-1, thus showing the noninferiority of tE2. The observed 5-year overall survival was 81.1% in the tE2 group and 79.2% in the LHRH agonist group, with a hazard ratio for death of 0.90 (95% CI, 0.75 to 1.07), favoring tE2 (Panel B). Shaded regions indicate 95% confidence intervals.

death were generally similar in the treatment groups.

Data on castrate levels of testosterone (<1.7 nmol per liter) during the first year of treatment were available for 1075 of 1082 patients in PATCH (Fig. 3A). The percentage of patients with a castrate level of testosterone at 1 month was higher in the tE2 group than in the LHRH agonist group owing to the absence of a temporary early increase in testosterone levels with tE2, whereas percentages in the two groups were similar at 3, 6, and 12 months.

Data from 1066 patients were assessed in the analysis of sustained castrate levels of testosterone during the first year after randomization; 16 patients (7 in the tE2 group and 9 in the LHRH agonist group) were excluded from the analysis because no testosterone levels were reported between day 35 and year 1 after randomization. Castrate levels of testosterone were sustained during the first year after randomization in 85% of the patients in each treatment group who were continuing the assigned treatment (Fig. 3B). The percentage of patients with sustained castrate levels of testosterone while continuing the assigned treatment during the 3-year period after randomization was also similar in the treatment groups. Results of the analyses of castrate levels of testosterone according to target testosterone level and brand of patch are shown in Table S4.

Mean levels of estradiol among patients receiving tE2 remained fairly constant (approximately 900 pmol per liter) during the first year after randomization (Table S3). Patients continued the assigned treatment for a median of 3.25 years (95% CI, 3.05 to 3.44) in the tE2 group and 4.27 years (95% CI, 3.95 to 4.58) in the LHRH agonist group. This difference was accounted for by the switch to LHRH agonists among some of the patients assigned to receive tE2, owing to toxic effects or disease progression (switching from LHRH agonists to tE2 patches did not occur because the patches were still under evaluation).

SAFETY

Adverse events during receipt of the assigned treatment are shown in Table 2. Adverse events of grade 3 or higher occurred in 110 of 693 patients (16%) in the tE2 group and in 117 of 612 (19%) of those in the LHRH agonist group. Adverse events related to low testosterone levels were similar in the treatment groups, with approximately 65% of the patients reporting erectile dysfunction and approximately 60% reporting decreased libido.

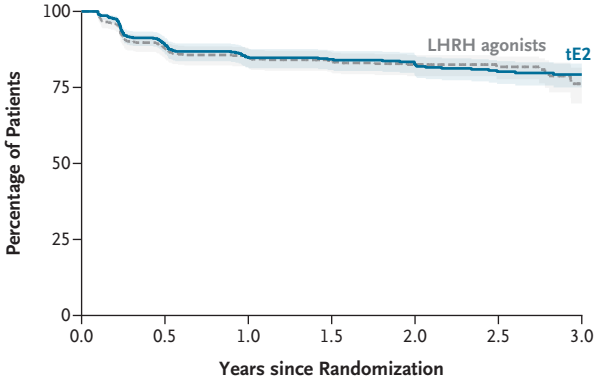
Differences between the treatment groups regarding the incidence of adverse events were as anticipated. Hot flashes occurred in 44% of

the patients in the tE2 group and in 89% of those in the LHRH agonist group (events of grade ≥2 occurred in 8% and 37%, respectively). Gynecomastia occurred in 85% of the patients in the tE2 group and in 42% of those in the LHRH agonist group (events of grade ≥2 occurred in 37% and 9%, respectively). Prophylactic breast irradiation was given in 46 of 576 patients (8%) in PATCH who received tE2; the incidence of gynecomastia during the treatment period was similar among those with irradiation (events of grade 0 or 1 occurred in 58% and those of grade 2 or 3 in 42%) and those without irradiation (events of grade 0 or 1 occurred in 59% and those of grade 2 or 3 in 41%). The incidence of pruritus was higher with tE2 than with LHRH agonists, whereas the incidence of insomnia and the incidence of fatigue were lower with tE2. Among the patients in PATCH who received tE2, at least one fracture had occurred in 2.8% by year 5 and in 5.1% by year 10; among those in PATCH who received LHRH agonists, at least one fracture had occurred in 5.8% and 10.5%, respectively.

A Castrate Level of Testosterone

	tE2	LHRH Agonists	Overall
	no. of patients with event/no. of patients (%)		
Baseline	1/581 (<1)	0/494 (0)	1/1075 (<1)
1 Month	418/506 (83)	215/360 (60)	633/866 (73)
3 Months	441/478 (92)	343/371 (92)	784/849 (92)
6 Months	429/471 (91)	371/401 (93)	800/872 (92)
12 Months	311/331 (94)	317/327 (97)	628/658 (95)

B Sustained Castrate Level of Testosterone



No. at Risk							
tE2	576	416	347	320	272	210	70
LHRH agonists	490	411	371	330	208	103	36

Figure 3. Castrate Levels of Testosterone.

Panel A shows the prevalence of castrate levels of testosterone during the first year after randomization, overall and according to assigned treatment. Panel B shows the prevalence of sustained castrate levels of testosterone among patients who were continuing the assigned treatment. Castrate levels of testosterone were sustained during the first year after randomization in 85% of the patients in each treatment group. Patients were included in the analysis if they had at least one reported testosterone level between day 35 and year 1 after randomization. Levels that were measured within 35 days after the start of treatment were excluded from the analysis to account for the initial increase in the testosterone level that may occur with LHRH agonists.

DISCUSSION

This analysis of a large dataset from two randomized trials shows that tE2 patches were noninferior to LHRH agonists for 3-year metastasis-free survival among men with high-risk nonmetastatic prostate cancer. The observed 5-year overall survival was 81.1% in the tE2 group and 79.2% in the LHRH agonist group (hazard ratio for death, 0.90; 95% CI, 0.75 to 1.07). The benefits of tE2 over LHRH agonists include reduced loss of bone mineral density, lower incidence of fracture, better metabolic profile, and lower incidence of hot flashes,[10,12,13] albeit with a higher incidence of gynecomastia. The side-effect profiles of LHRH agonists and tE2, along with the routes of administration, can inform patient choice regarding androgen-deprivation therapy and should be incorporated into discussions between patients and physicians before the start of treatment. The need for more information and educational programs about androgen-deprivation therapy for patients and their families has been highlighted.[4,21]

The effectiveness of reducing the serum testosterone level to control the growth of prostate cancer was first recognized by Huggins and Hodges.[22] Surgical castration and oral estrogen therapy[8] were used to reduce testosterone levels before the advent of LHRH agonists in the 1980s.[23] Current pharmaceutical options for androgen-deprivation therapy include injectable depot LHRH agonists, injectable or oral LHRH antagonists,[20,24] and now tE2 patches.

To inform decisions about androgen-deprivation therapy, several factors should be considered. First, the views of the patient are important. Data from focus groups suggest that patients will have a preferred approach to androgen-deprivation therapy for practical reasons (particularly the avoidance of injections) and emotional reasons.[25] Reductions in serum estradiol levels that accompany injectable and oral LHRH analogues cause

Table 2. Adverse Events during Receipt of the Assigned Treatment.*

Event	tE2 (N=693)				LHRH Agonists (N=612)			
	No Event	Grade 1	Grade 2	Grade 3 or 4	No Event	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Gynecomastia	105 (15)	329 (47)	226 (33)	33 (5)	357 (58)	199 (33)	47 (8)	9 (1)
Hot flashes	387 (56)	252 (36)	51 (7)	3 (<1)	70 (11)	316 (52)	195 (32)	31 (5)
Anemia	518 (75)	161 (23)	13 (2)	1 (<1)	401 (66)	182 (30)	25 (4)	4 (1)
Anxiety	519 (75)	154 (22)	20 (3)	0	424 (69)	154 (25)	32 (5)	2 (<1)
Chest pain	646 (93)	39 (6)	5 (1)	3 (<1)	550 (90)	45 (7)	10 (2)	7 (1)
Concentration impairment	559 (81)	120 (17)	12 (2)	2 (<1)	462 (75)	128 (21)	18 (3)	4 (1)
Depression	537 (77)	136 (20)	18 (3)	2 (<1)	442 (72)	137 (22)	30 (5)	3 (<1)
Dizziness	582 (84)	101 (15)	9 (1)	1 (<1)	474 (77)	124 (20)	13 (2)	1 (<1)
Erectile dysfunction	244 (35)	240 (35)	184 (27)	25 (4)	220 (36)	215 (35)	145 (24)	32 (5)
Fatigue	225 (32)	355 (51)	106 (15)	7 (1)	126 (21)	330 (54)	147 (24)	9 (1)
Insomnia	483 (70)	186 (27)	20 (3)	4 (1)	353 (58)	204 (33)	52 (8)	3 (<1)
Increased irritability	525 (76)	155 (22)	13 (2)	0	439 (72)	153 (25)	17 (3)	3 (<1)
Decreased libido	293 (42)	238 (34)	154 (22)	8 (1)	253 (41)	222 (36)	125 (20)	12 (2)
Nausea	624 (90)	64 (9)	4 (1)	1 (<1)	528 (86)	76 (12)	7 (1)	1 (<1)
Pruritus	384 (55)	268 (39)	36 (5)	5 (1)	493 (81)	106 (17)	13 (2)	0

* Data are for patients in the safety analysis, which included all the patients who received the trial treatment and reported adverse events on a form during at least one follow-up visit. Adverse events were graded according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events in patients who were recruited at PATCH trial sites and according to version 4.0 in those who were recruited at STAMPEDE-1 trial sites. The maximum severity for each adverse event is shown. Percentages may not sum to 100 because of rounding.

many of the adverse events associated with androgen-deprivation therapy (Fig. S3).[6] Hot flashes burden many patients with prostate cancer, leading to substantial adverse effects on quality of life.[26] In a randomized cohort of 737 men, the mean quality-of-life score was higher among the patients receiving tE2 than among those receiving LHRH agonists; this finding was attributed to fewer hot flashes, a lower level of fatigue, and better physical function.[13] Overall, 8% of the patients receiving tE2 as compared with 46% of those receiving LHRH agonists were "quite a bit" or "very" bothered by hot flashes. The incidence of gynecomastia as reported by the patient was 37% among the patients receiving tE2 as compared with 5% among those receiving LHRH agonists, findings that are consistent with the data reported here.

A second consideration is whether the mode of androgen-deprivation therapy is compatible with other currently recommended treatments. Standard care has evolved during evaluation of the tE2 patches, with radiotherapy to the prostate and docetaxel now given concomitantly with conventional androgen-deprivation therapy.[16,17] These therapeutic advances were incorporated into our trials, with enhanced monitoring in the tE2 group to ensure that excess adverse events did not result from concomitant use of radiotherapy or docetaxel. Most recently, androgen-receptor pathway inhibitors (ARPIs) have been introduced.[27] The use of ARPIs in combination with tE2 or LHRH agonists was assessed in patients with metastasis stage M1 prostate cancer who were recruited through the PATCH or STAMPEDE-1 trial network.[28] The proportion of patients with a PSA response, as defined by a nadir PSA level of 2 ng per milliliter or less during the first 6 months of concomitant treatment with ARPIs, was similar in the tE2 and LHRH agonist groups.

A third consideration is longer-term health

outcomes after the diagnosis and treatment of prostate cancer. Loss of bone mineral density and subsequent osteoporosis due to current androgen-deprivation therapy is associated with substantial morbidity and mortality.[29] In an assessment of the change in bone mineral density by means of dual-energy x-ray absorptiometry in 74 patients with prostate cancer, the mean percentage change from baseline to year 1 was 6.0% among men receiving tE2 as compared with –1.4% among those receiving LHRH agonists (P<0.001).[12] Strategies to mitigate loss of bone mineral density during androgen-deprivation therapy include the addition of bone-strengthening agents such as bisphosphonates.[30] However, this approach increases polypharmacy and treatment costs, with real-world data indicating that adverse effects of androgen-deprivation therapy on bone health are poorly managed.[31] The incidence of prostate cancer is increasing in low- and middle-income countries,[32] and a treatment that has low costs and few toxic effects, is administered by the patient, and mitigates the need for bone-protection agents is an attractive option in these areas, as well as in high-income countries. Example comparative costs are provide in the Supplementary Appendix.

Strengths of our trial include the adaptive design and the extended follow-up period. These factors allowed for long-term monitoring of adverse events and confirmation of our original hypothesis that parenteral administration of estradiol will provide the benefits of estrogen while avoiding its cardiovascular thromboembolic side effects in patients with prostate cancer.[10] Limitations of the current trial include the introduction of prostate radiotherapy as standard care and changes in the duration of androgen-deprivation therapy and systemic treatments during the trial period.[33] The median duration of treatment was shorter among patients in the tE2 group than among those in the LHRH agonist group. The switch from tE2 therapy to LHRH agonist treatment because of toxic effects or disease progression accounted for this difference but showed that patients can transition from one type of androgen-deprivation therapy to another if they have clinically significant adverse events. Only 8% of the patients received prophylactic breast irradiation, which did not appear to have reduced the incidence of gynecomastia. Comparative data on the recovery of testosterone levels are not available. Data on quality-of-life measures were collected with the use of validated questionnaires but have not yet been analyzed. Finally, we acknowledge that other formulations of tE2 exist, such as gels, that could be used for androgen-deprivation therapy.[34]

We found that tE2 patches were effective in achieving castrate levels of testosterone and were noninferior to LHRH agonists regarding metastasis-free survival. The incidence of hot flashes, which can be debilitating, was lower with tE2 than with LHRH agonists. Fracture occurred in a smaller percentage of patients in the tE2 group than in the LHRH agonist group, and the incidence of gynecomastia was higher with tE2. Given these findings, tE2 patches can be considered an alternative choice for testosterone suppression in men with metastasis stage M0 and nodal stage N0 or N+ prostate cancer. The patches appear to be as effective as standard LHRH agonists against prostate cancer and are associated with a lower incidence of the short-term and long-term deleterious adverse events related to estrogen depletion during treatment with LHRH agonists.

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