ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

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ABSTRACT

BACKGROUND

Abiraterone acetate plus prednisolone improves survival in men with relapsed prostate cancer. We assessed the effect of this combination in men starting long-term androgen-deprivation therapy (ADT), using a multigroup, multistage trial design.

METHODS

We randomly assigned patients in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate (1000 mg daily) and prednisolone (5 mg daily) (combination therapy). Local radiotherapy was mandated for patients with node-negative, nonmetastatic disease and encouraged for those with positive nodes. For patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until radiologic, clinical, or prostate-specific antigen (PSA) progression; otherwise, treatment was to continue for 2 years or until any type of progression, whichever came first. The primary outcome measure was overall survival. The intermediate primary outcome was failure-free survival (treatment failure was defined as radiologic, clinical, or PSA progression or death from prostate cancer).

RESULTS

A total of 1917 patients underwent randomization from November 2011 through January 2014. The median age was 67 years, and the median PSA level was 53 ng per milliliter. A total of 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate nonmetastatic disease, and 28% had node-negative, nonmetastatic disease; 95% had newly diagnosed disease. The median follow-up was 40 months. There were 184 deaths in the combination group as compared with 262 in the ADT-alone group (hazard ratio, 0.63; 95% confidence interval [CI], 0.52 to 0.76; P<0.001); the hazard ratio was 0.75 in patients with nonmetastatic disease and 0.61 in those with metastatic disease. There were 248 treatment-failure events in the combination group as compared with 535 in the ADT-alone group (hazard ratio, 0.29; 95% CI, 0.25 to 0.34; P<0.001); the hazard ratio was 0.21 in patients with nonmetastatic disease and 0.31 in those with metastatic disease. Grade 3 to 5 adverse events occurred in 47% of the patients in the combination group (with nine grade 5 events) and in 33% of the patients in the ADT-alone group (with three grade 5 events).

CONCLUSIONS

Among men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone. (Funded by Cancer Research U.K. and others; STAMPEDE ClinicalTrials.gov number, NCT00268476, and Current Controlled Trials number, ISRCTN78818544.)

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THE SYSTEMIC THERAPY IN ADVANCING or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial recruits patients commencing long-term androgen-deprivation therapy (ADT; orchiectomy or gonadotropin-releasing hormone [GnRH] agonists or antagonists) for the first time for locally advanced or metastatic prostate cancer. Several agents have improved overall survival (docetaxel, abiraterone acetate, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T)[1-8] or reduced morbidity (zoledronic acid and denosumab)[9-11] among such patients. These agents were initially investigated in men with very advanced disease whose tumors had progressed during first-line ADT, a disease state now termed castration-resistant prostate cancer.

The STAMPEDE trial uses a novel multigroup, multistage (also called multiarm, multistage [MAMS]) platform design[12-14] to test whether the addition of further treatments to ADT improves overall survival if used in the first-line setting. It uses intermediate activity analyses, based on failure-free survival, to cease randomization to research groups that are insufficiently active.[12-14] We have previously reported that treatment with docetaxel at the inception of ADT increased median survival from 71 months to 81 months as well as overall survival (hazard ratio for death, 0.76).[15,16] These results, along with those of a systematic review that included other trials[17-19] and of a meta-analysis,[16] led to docetaxel becoming a part of the standard of care for suitable patients with prostate cancer who had not received previous hormone therapy.

An important mechanism for escape from tumor control by androgen ablation includes the intracellular conversion of steroid precursors to androgenic steroids by prostate-cancer cells. Abiraterone acetate is a selective, irreversible inhibitor of CYP17, an enzyme that is critical in the production of androgens in the testes, adrenal glands, and prostate-tumor tissue. Inhibition of CYP17 in combination with ADT results in a more effective androgen depletion than can be induced by surgical castration or by GnRH analogues alone.[20] Two large, phase 3 trials showed that the addition of abiraterone acetate with prednisolone to standard-of-care therapy prolonged survival among men with castration-resistant prostate cancer.[4,5,21] The STAMPEDE trial is investigating whether the earlier use of abiraterone in men who are initiating long-term ADT could improve survival.

METHODS

TRIAL DESIGN AND PATIENTS

We used a multigroup, multistage platform design, incorporating a seamless phase 2–3 component. The primary outcome was overall survival, defined as the time from randomization to death from any cause. The intermediate primary outcome was failure-free survival, defined as the time to the first of the following forms of treatment failure: biochemical (prostate-specific antigen [PSA]) failure (see the protocol, available with the full text of this article at NEJM.org); progression of local, lymph-node, or distant metastases; or death from prostate cancer. Secondary outcome measures included adverse events, symptomatic skeletal events, progression-free survival (i.e., failure-free survival excluding biochemical failure), prostate cancer–specific survival, and (data not shown) quality of life.

The rationale and design were described previously.[12-14,22] Full details are provided in the protocol. In summary, eligible patients had prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: a tumor stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng per milliliter) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (in men no longer receiving therapy, a PSA level >4 ng per milliliter with a doubling time of <6 months, a PSA level >20 ng per milliliter, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment). Patients were intended for treatment with long-term ADT that started no longer than 12 weeks before randomization. There were no age restrictions. Patients with clinically significant cardiovascular disease (e.g., severe angina, recent myocardial infarction, or a history of cardiac failure) were excluded.

TRIAL OVERSIGHT AND CONDUCT

The trial was sponsored by the U.K. Medical Research Council (MRC) and conducted by the MRC Clinical Trials Unit at University College

London (UCL). MRC provided funding for the trial through core funding to UCL. Cancer Research U.K. approved the trial design and subsequent amendments and provided funding support but had no further input. Janssen approved the design for this comparison (ADT plus abiraterone and prednisolone vs. ADT alone) and participated in discussions on the progress of the trial. Janssen also provided grant funding, abiraterone acetate, and funds for drug distribution. Representatives from Janssen were invited to comment on the manuscript. Further funding for the platform was provided by Astellas Pharma, Clovis Oncology, Novartis, Pfizer, and Sanofi Aventis. The trial was conducted in accordance with the principles of Good Clinical Practice guidelines and the Declaration of Helsinki, and the appropriate regulatory and ethics approvals were obtained. All the patients provided written informed consent.

The analyses were driven by prespecified criteria, and the decision to submit the manuscript for publication was made by the members of the Trial Management Group. Three authors at the MRC Clinical Trials Unit at UCL accessed the raw data; processed data that were released by the independent data monitoring committee and trial steering committee were available to all the co-authors. The authors vouch for the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

RANDOMIZATION AND MASKING

Randomization was performed centrally by telephone with the use of a computerized algorithm, which was developed and maintained by the MRC Clinical Trials Unit at UCL. Minimization with a random element of 80% was used, with stratification according to randomizing center, age at randomization (<70 vs. ≥70 years), the presence or absence of metastases, planned use of prostate radiotherapy (yes vs. no), nodal involvement (negative vs. indeterminate vs. positive), World Health Organization performance status (0 vs. 1 or 2 [on a scale of 0 to 4, with higher numbers indicating greater disability]), type of ADT, and regular, long-term use of aspirin or nonsteroidal antiinflammatory drugs (yes vs. no). The assignment ratio was 1:1 to standard of care alone or with abiraterone acetate and prednisolone (combi-

nation therapy). The comparison was open-label, because masking of the treatment assignment was deemed impracticable. Eligible patients could be assigned to any of the trial groups that were open; we focus here on patients assigned contemporaneously to ADT alone or with abiraterone and prednisolone.

PROCEDURES

ADT was given for at least 2 years; radiotherapy at 6 to 9 months after randomization was mandatory for patients with node-negative, nonmetastatic disease and optional for patients with node-positive, nonmetastatic disease. Abiraterone (1000 mg) with prednisolone (5 mg) was given once daily. The treatment duration depended on disease stage and intent for radical radiotherapy: for patients with nonmetastatic disease with no radiotherapy planned and for patients with metastatic disease, treatment continued until PSA, radiologic, or clinical progression or until another treatment was started; for patients with nonmetastatic disease with radiotherapy planned, treatment was to continue for 2 years or until any type of progression, whichever came first. Dose modifications are described in the protocol.

Patients were assessed every 6 weeks during the first 6 months, then every 12 weeks until 2 years, then every 6 months until 5 years, and then annually; in addition, patients receiving combination therapy were assessed at least every 3 months. Assessments included PSA testing and ascertainment of adverse events; further tests were conducted at the discretion of the treating physician. The nadir PSA level (for the definition of PSA progression) was defined as the lowest level within 24 weeks after randomization. There was no protocol-mandated imaging except at baseline. Adverse events were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events (initially, version 3.0; later, version 4.0). Serious adverse events and reactions were reported accordingly.

STATISTICAL ANALYSIS

The sample size was calculated with the use of Stata nstage and predecessor programs that allow for the design of multigroup, multistage trials.[23] Assuming a median failure-free survival of 2 years and a median overall survival between 4 and 5 years for ADT, we targeted a 25% relative difference between the combination group and the

ADT-alone group for both failure-free survival (hazard ratio for treatment failure, 0.75) and overall survival (hazard ratio for death, 0.75). The main analysis for the comparison of combination therapy against control for survival could be performed after the occurrence of approximately 267 deaths in the control group for 90% power and a one-sided alpha level of 2.5%, after we accounted for three intermediate lack-of-benefit analyses of failure-free survival. An independent data monitoring committee reviewed accumulating data, guided by lack-of-benefit stopping guidelines.

Data on patients without an event of interest were censored when they were last known to be event-free. The median follow-up was determined through reversing death and censoring indicators. Standard survival-analysis methods were used to analyze time-to-event data in Stata software, version 14, with Kaplan–Meier estimates for survival curves and Cox proportional-hazards models to estimate relative treatment effects. These estimates were adjusted for stratification factors (except randomizing center and ADT method) and were stratified according to time periods defined by corecruiting groups. A hazard ratio of less than 1.00 favored the combination group. The restricted mean survival time (restricted to 54 months) was calculated from flexible parametric models (5 degrees of freedom). The proportional-hazards assumption was tested; the restricted mean survival time was emphasized in the presence of nonproportionality. All the confidence intervals are at the 95% level. Prespecified subgroup analyses looked at the consistency of treatment effect according to stratification factors, time period, categorized Gleason score, and quintiles of PSA levels that were measured before the initiation of long-term ADT. Key subgroup analyses according to metastatic status were prespecified. Exploratory analyses considered prostate cancer–specific survival and progression-free survival according to the age at randomization.

All the patients were included in the efficacy analyses under their assigned treatment on an intention-to-treat basis. For safety analyses, patients were grouped according to the treatment that they started. In the analysis of the median duration of abiraterone treatment, data were censored at the date of last contact with the patient if the patient had not reported stopping the drug.

RESULTS

PATIENTS

Between November 15, 2011, and January 17, 2014, a total of 1917 consenting patients at 111 U.K. and 5 Swiss sites underwent randomization (957 to ADT alone and 960 to combination therapy). Data were frozen on February 10, 2017. The flow of patients through the trial is shown in Figure S1 in the Supplementary Appendix, available at NEJM.org; the baseline characteristics of the patients are shown in Table 1, and in Table S1 in the Supplementary Appendix. The median PSA level was 53 ng per milliliter. The median follow-up was 40 months.

TREATMENT

The median time from randomization to the initiation of abiraterone was 1.3 weeks, and the median time from the initiation of ADT to the initiation of abiraterone was 8.0 weeks (most patients started ADT before randomization) (Table S2 in the Supplementary Appendix). Of the 960 patients in the combination group, 10 (1%) did not receive abiraterone, mostly because they declined treatment. The median duration of abiraterone treatment was 23.7 months in the patients for whom the duration was capped at 2 years (67% reported stopping for treatment completion) and 33.2 months in the patients who could continue through progression (51% reported permanent stopping for progression and 20% for excessive toxic effects) (Table S2 and Fig. S2 in the Supplementary Appendix). A total of 265 patients (28%) had not yet permanently stopped treatment with abiraterone at the time of this report.

The planned rate of use of radiotherapy was 41% in the combination group and in the ADT-alone group. The reported rate of use of radiotherapy was 39% in the combination group and 40% in the ADT-alone group.

OVERALL SURVIVAL

There were 184 deaths in the combination group and 262 in the ADT-alone group. There was strong evidence of a survival advantage in the combination group, with a 3-year survival of 83% as compared with 76% in the ADT-alone group (hazard ratio for death, 0.63; 95% confidence interval [CI], 0.52 to 0.76; P<0.001) (Fig. 1A). There was no evidence of nonproportional haz-

Table 1. Characteristics of the Patients.*

Characteristic	ADT Alone (N=957)	Combination Therapy (N=960)
Age at randomization — yr		
Median (IQR)	67 (62 to 72)	67 (63 to 72)
Range	39 to 84	42 to 85
PSA level before ADT — ng/ml		
Median (IQR)	56 (19 to 165)	51 (19 to 158)
Range	0 to 10,530	0 to 21,460
WHO performance status — no. (%)†		
0	744 (78)	745 (78)
1 or 2	213 (22)	215 (22)
Disease group — no. (%)		
Newly diagnosed node-negative, nonmetastatic disease	256 (27)	253 (26)
Newly diagnosed node-positive, nonmetastatic disease	187 (20)	182 (19)
Newly diagnosed metastatic disease	476 (50)	465 (48)
Previously treated nonmetastatic disease	12 (1)	25 (3)
Previously treated metastatic disease	26 (3)	35 (4)
Gleason score — no. (%)‡		
≤7	223 (23)	221 (23)
8 to 10	721 (75)	715 (74)
Unknown	13 (1)	24 (2)
Planned or current long-term ADT — no. (%)		
Orchiectomy	5 (1)	3 (<1)
Bicalutamide	5 (1)	5 (1)
Dual androgen blockade	4 (<1)	1 (<1)
LHRH-based§	943 (99)	951 (99)
Time to initiation of ADT from randomization — days¶		
Median (IQR)	−45 (−67 to −23)	−44 (−63 to −24)
Range	−85 to 39	−85 to 28
Planned antiandrogen use — no. (%)		
No	50 (5)	61 (6)
Short-term antiandrogen	902 (94)	895 (93)
Long-term antiandrogen	5 (1)	4 (<1)
Radiotherapy planned — no. (%)‖		
No	561 (59)	564 (59)
Yes	396 (41)	396 (41)
Hypertension — no. (%)		
No	571 (60)	557 (58)
Yes, but still fit for trial	385 (40)	401 (42)
Cardiovascular assessment not received	1 (<1)	2 (<1)

* Combination therapy was androgen-deprivation therapy (ADT) plus abiraterone acetate and prednisolone. Percentages may not sum to 100 because of rounding. IQR denotes interquartile range, and PSA prostate-specific antigen.
† The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.
‡ Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis.
§ All patients with planned use of luteinizing hormone–releasing hormone (LHRH) analogues should have antiandrogens for disease flares, at least.
¶ Data were missing for one patient in the ADT-alone group.
‖ Radiotherapy was mandated for patients with newly diagnosed node-negative, nonmetastatic disease and strongly encouraged in patients with newly diagnosed node-positive, nonmetastatic disease.

ards (P=0.31) or of heterogeneity of the treatment effect according to metastatic status at randomization. A preplanned subgroup analysis of 1002 patients with metastatic disease at entry included 368 deaths (Fig. 1C). The same comparisons in patients without metastatic disease at randomization are immature, currently with 78 deaths in total (Fig. 1E). There was no evidence of heterogeneity of effect in other subgroups (Fig. 2A).

FAILURE-FREE SURVIVAL

There were 248 events of treatment failure (radiologic, clinical, or PSA progression or death from prostate cancer) in the combination group and 535 in the ADT-alone group. The 3-year failure-free survival was 75% in the combination group and 45% in the ADT-alone group (hazard ratio for treatment failure, 0.29; 95% CI, 0.25 to 0.34; P<0.001) (Fig. 1B). There was evidence of nonproportional hazards (P=0.001), so we present restricted mean failure-free survival time: 43.9 months in the combination group and 30.0 months in the ADT-alone group in the first 54 months after randomization, a difference of 13.9 months (95% CI, 12.3 to 15.4). The effect of abiraterone on failure-free survival was noted in all subgroups (Fig. 1D and 1F and Fig. 2B).

OTHER EFFICACY OUTCOME MEASURES

There were 198 events of radiologic or clinical progression or death from prostate cancer in the combination group and 379 in the ADT-alone group. The 3-year progression-free survival was 80% in the combination group and 62% in the ADT-alone group (hazard ratio for clinical or radiologic progression or death from prostate cancer, 0.40; 95% CI, 0.34 to 0.47; P<0.001) (Fig. S3 in the Supplementary Appendix). There were 113 symptomatic skeletal events reported so far in the combination group and 203 in the ADT-alone group. The 3-year rate without symptomatic skeletal events was 88% in the combination group and 78% in the ADT-alone group (hazard ratio for symptomatic skeletal events, 0.46; 95% CI, 0.37 to 0.58; P<0.001) (Fig. S4A in the Supplementary Appendix). This difference was most marked in the subgroup of patients with metastatic disease (Fig. S4B in the Supplementary Appendix). A total of 140 of the 184 deaths in the combination group (76%) and 216 of the 262 deaths in the ADT-alone group (82%) were attrib-

uted to prostate cancer on central review. The competing-risks subhazard ratio for death from prostate cancer was 0.58 (95% CI, 0.47 to 0.72).

EXPLORATORY ANALYSES

Exploratory analyses that considered the outcomes of progression-free and prostate cancer–specific survival within subgroups of age at randomization suggested a favorable treatment effect regardless of age; proportionally fewer events were noted in older patients. In patients younger than 70 years of age, there were 113 events of radiologic or clinical progression or death from prostate cancer in the combination group and 263 in the ADT-alone group (hazard ratio, 0.36; 95% CI, 0.29 to 0.45); in patients 70 years of age or older, there were 65 events in the combination group and 116 in the ADT-alone group (hazard ratio, 0.50; 95% CI, 0.37 to 0.68; P=0.10 for interaction). In patients younger than 70 years of age, there were 93 deaths from prostate cancer in the combination group and 154 in the ADT-alone group (subhazard ratio, 0.51; 95% CI, 0.39 to 0.66); in patients 70 years of age or older, there were 47 deaths from prostate cancer in the combination group and 62 in the ADT-alone group (subhazard ratio, 0.80; 95% CI, 0.54 to 1.17; P=0.08 for interaction).

ADVERSE EVENTS

Patients in the safety population who reported adverse events of grade 3 or higher during their entire time in the trial numbered 443 of 948 (47%) in the combination group and 315 of 960 (33%) in the ADT-alone group (Table 2). There were 12 grade 5 adverse events, including 9 in the combination group (2 events of pneumonia [1 including sepsis], 2 events of stroke, and 1 event each of dyspnea, lower respiratory tract infection, liver failure, pulmonary hemorrhage, and chest infection) and 3 in the ADT-alone group (2 events of myocardial infarction and 1 event of bronchopneumonia). Among the 1476 patients in the safety population in whom progression had not occurred within the first year, the prevalence of adverse events of grade 3 or higher was 15% in the combination group and 11% in the ADT-alone group. The main additional adverse events over and above the control therapy were hypertension, mild increases in aminotransferase levels, and respiratory disorders. Further details, including an overview according to age, are provided
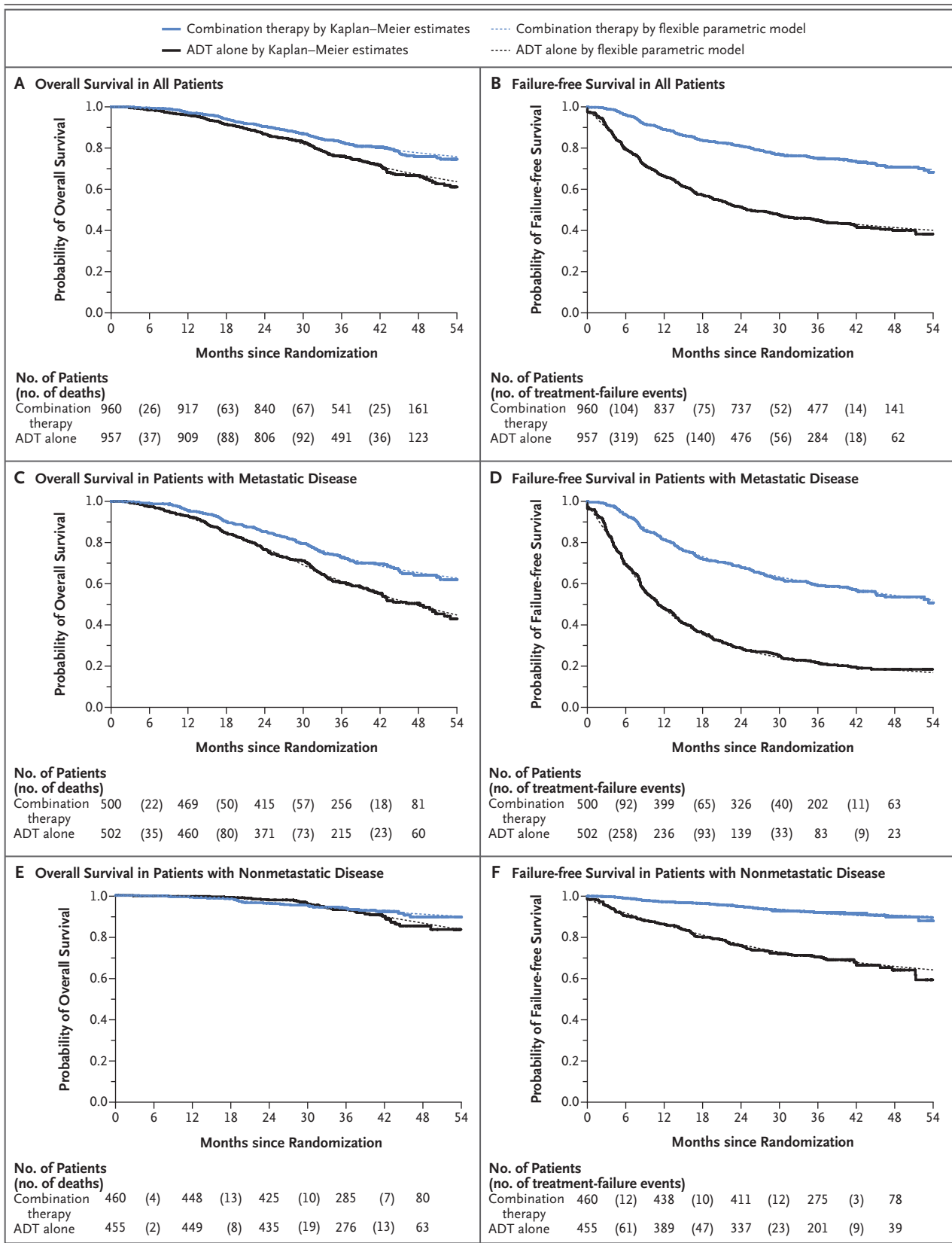
Combination therapy by Kaplan–Meier estimates
ADT alone by Kaplan–Meier estimates
Combination therapy by flexible parametric model
ADT alone by flexible parametric model

A Overall Survival in All Patients

Probability of Overall Survival

Months since Randomization

No. of Patients
(no. of deaths)

Combination therapy	960	(26)	917	(63)	840	(67)	541	(25)	161
ADT alone	957	(37)	909	(88)	806	(92)	491	(36)	123

B Failure-free Survival in All Patients

Probability of Failure-free Survival

Months since Randomization

No. of Patients
(no. of treatment-failure events)

Combination therapy	960	(104)	837	(75)	737	(52)	477	(14)	141
ADT alone	957	(319)	625	(140)	476	(56)	284	(18)	62

C Overall Survival in Patients with Metastatic Disease

Probability of Overall Survival

Months since Randomization

No. of Patients
(no. of deaths)

Combination therapy	500	(22)	469	(50)	415	(57)	256	(18)	81
ADT alone	502	(35)	460	(80)	371	(73)	215	(23)	60

D Failure-free Survival in Patients with Metastatic Disease

Probability of Failure-free Survival

Months since Randomization

No. of Patients
(no. of treatment-failure events)

Combination therapy	500	(92)	399	(65)	326	(40)	202	(11)	63
ADT alone	502	(258)	236	(93)	139	(33)	83	(9)	23

E Overall Survival in Patients with Nonmetastatic Disease

Probability of Overall Survival

Months since Randomization

No. of Patients
(no. of deaths)

Combination therapy	460	(4)	448	(13)	425	(10)	285	(7)	80
ADT alone	455	(2)	449	(8)	435	(19)	276	(13)	63

F Failure-free Survival in Patients with Nonmetastatic Disease

Probability of Failure-free Survival

Months since Randomization

No. of Patients
(no. of treatment-failure events)

Combination therapy	460	(12)	438	(10)	411	(12)	275	(3)	78
ADT alone	455	(61)	389	(47)	337	(23)	201	(9)	39

Figure 1 (facing page). Overall Survival and Failure-free Survival in All Patients and According to Metastatic Status at Randomization (Intention-to-Treat Population).

Combination therapy was androgen-deprivation therapy (ADT) plus abiraterone acetate and prednisolone. Treatment failure was defined as radiologic, clinical, or prostate-specific antigen (PSA) progression or death from prostate cancer.

in Tables S4 through S32 in the Supplementary Appendix. The pattern and levels of adverse events were similar in the intention-to-treat population.

TREATMENT AFTER PROGRESSION

There are emerging differences in the therapies used at relapse (Fig. 3, and Table S3 in the Supplementary Appendix). The median time from relapse to life-prolonging therapy for castration-resistant prostate cancer (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium-223) or any subsequent therapy was similar in the two groups, but absolute numbers of patients reporting life-prolonging or any treatment after progression were higher in the ADT-alone group than in the combination group (ADT-alone group, 310 and 477, respectively, of 957 patients; combination group, 131 and 196, respectively, of 960 patients). The use of abiraterone at relapse in patients who received abiraterone as primary therapy was lower in patients in the combination group than in patients in the ADT-alone group; patients in the combination group could continue abiraterone beyond the first event of radiologic, clinical, or PSA progression until all three protocol-defined progression types were reached. The rate of docetaxel use was proportionately higher in the combination group than in the ADT-alone group. Because 1471 of the men (77%) in this comparison remain alive, these data will evolve with time as more patients have a relapse and receive further treatments.

DISCUSSION

STAMPEDE is a multigroup, multistage platform trial protocol investigating the efficacy of additional therapy at the time of inception of primary ADT in men with newly diagnosed, locally advanced, or metastatic disease or in those with relapsing disease and poor prognostic features. This is the sixth comparison in the trial for which we are reporting survival data[15,16,24-27] and the first comparison incorporated after trial initiation.[22]

The use of ADT plus abiraterone and prednisolone as compared with ADT alone was associated with a 71% relative improvement in the time to treatment failure, which translated into a 37% difference in overall survival. These findings were consistent in patients with metastatic disease and those with nonmetastatic disease, although most deaths have occurred in the patients with metastatic disease. The between-group difference in survival among the patients with nonmetastatic disease, which is underpinned by a large difference in failure-free survival, occurred even though abiraterone was administered for 2 years or less in this group.

There was good adherence to abiraterone, which was associated with acceptable adverse-event rates, with most patients stopping therapy owing to the completion of planned therapy or protocol-defined progression rather than toxic effects. Adverse events were in line with previous experience in castration-resistant prostate cancer,[4,5,21] despite the longer absolute duration of therapy, particularly in the patients with metastatic disease. Nearly 300 patients are still receiving treatment. Few patients stopped treatment because of side effects, but there were more grade 3 to 5 adverse events reported in the combination group than in the ADT-alone group. The lower dose of prednisolone that was used does not seem to have influenced the rate of pharmacologically relevant severe adverse events, such as hypertension or hypokalemia.[20]

The strengths of the comparison in this trial include broad recruitment through an academic network (116 centers, including most U.K. oncology centers, in collaboration with the Swiss Group for Clinical Cancer Research) encompassing a wide range of disease states. The size of the trial permits some examination of interactions, including those with other treatments known to be effective (e.g., radiotherapy) and prognostic factors used for stratification at randomization. Effects in all subgroups were similar, with no evidence of heterogeneity. The apparent inconsistency in survival-effect size in men 70 years of age or older is probably an artifact arising from a small number of events; the absolute difference is only 8 deaths (74 in the combination group and 82 in the ADT-alone group). The result is complicated by a higher risk
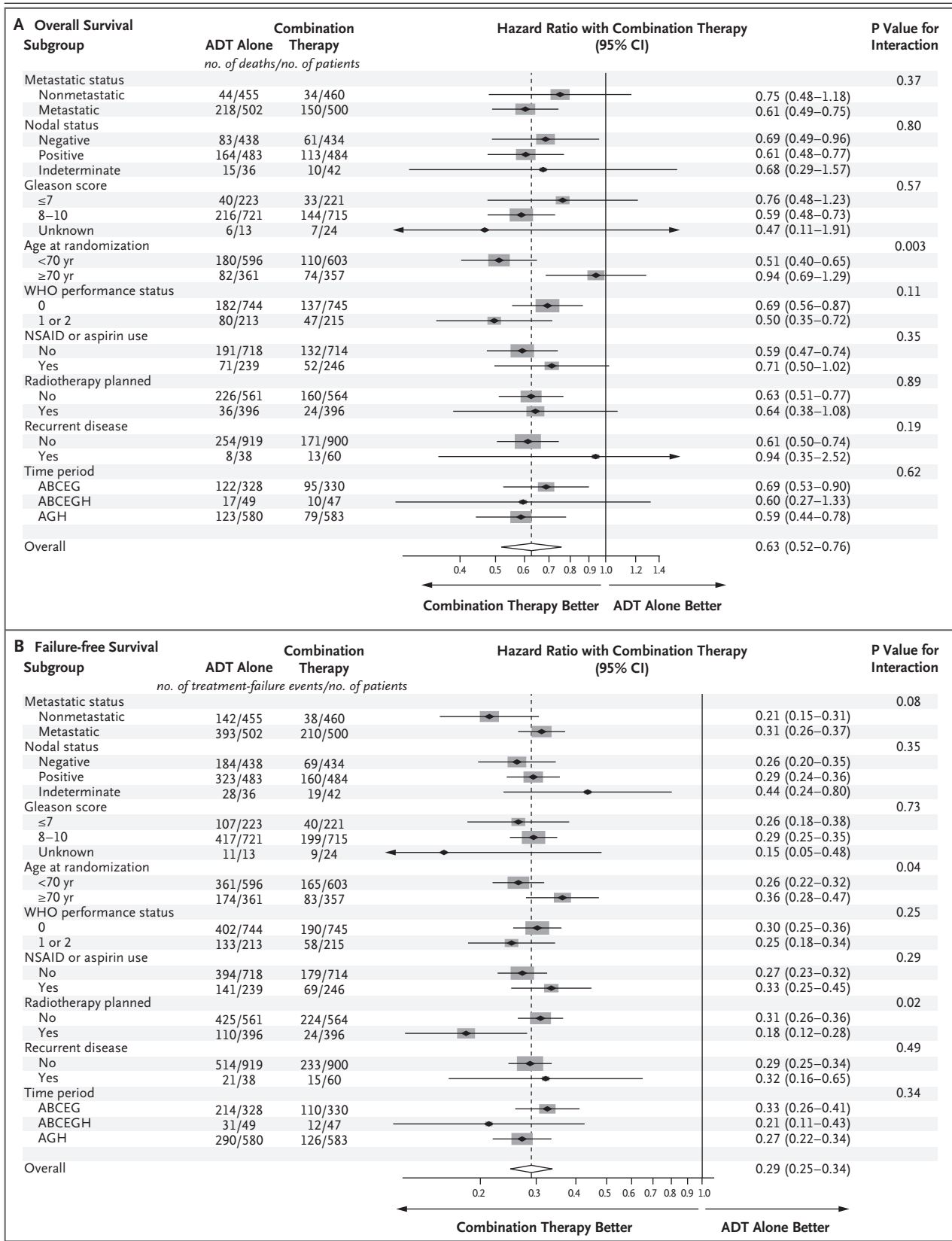
A Overall Survival

Subgroup	ADT Alone	Combination Therapy	Hazard Ratio with Combination Therapy (95% CI)	P Value for Interaction
	no. of deaths/no. of patients			
Metastatic status				0.37
Nonmetastatic	44/455	34/460	0.75 (0.48–1.18)	
Metastatic	218/502	150/500	0.61 (0.49–0.75)	
Nodal status				0.80
Negative	83/438	61/434	0.69 (0.49–0.96)	
Positive	164/483	113/484	0.61 (0.48–0.77)	
Indeterminate	15/36	10/42	0.68 (0.29–1.57)	
Gleason score				0.57
≤7	40/223	33/221	0.76 (0.48–1.23)	
8–10	216/721	144/715	0.59 (0.48–0.73)	
Unknown	6/13	7/24	0.47 (0.11–1.91)	
Age at randomization				0.003
<70 yr	180/596	110/603	0.51 (0.40–0.65)	
≥70 yr	82/361	74/357	0.94 (0.69–1.29)	
WHO performance status				0.11
0	182/744	137/745	0.69 (0.56–0.87)	
1 or 2	80/213	47/215	0.50 (0.35–0.72)	
NSAID or aspirin use				0.35
No	191/718	132/714	0.59 (0.47–0.74)	
Yes	71/239	52/246	0.71 (0.50–1.02)	
Radiotherapy planned				0.89
No	226/561	160/564	0.63 (0.51–0.77)	
Yes	36/396	24/396	0.64 (0.38–1.08)	
Recurrent disease				0.19
No	254/919	171/900	0.61 (0.50–0.74)	
Yes	8/38	13/60	0.94 (0.35–2.52)	
Time period				0.62
ABCEG	122/328	95/330	0.69 (0.53–0.90)	
ABCEGH	17/49	10/47	0.60 (0.27–1.33)	
AGH	123/580	79/583	0.59 (0.44–0.78)	
Overall			0.63 (0.52–0.76)	

Combination Therapy Better — ADT Alone Better

B Failure-free Survival

Subgroup	ADT Alone	Combination Therapy	Hazard Ratio with Combination Therapy (95% CI)	P Value for Interaction
	no. of treatment-failure events/no. of patients			
Metastatic status				0.08
Nonmetastatic	142/455	38/460	0.21 (0.15–0.31)	
Metastatic	393/502	210/500	0.31 (0.26–0.37)	
Nodal status				0.35
Negative	184/438	69/434	0.26 (0.20–0.35)	
Positive	323/483	160/484	0.29 (0.24–0.36)	
Indeterminate	28/36	19/42	0.44 (0.24–0.80)	
Gleason score				0.73
≤7	107/223	40/221	0.26 (0.18–0.38)	
8–10	417/721	199/715	0.29 (0.25–0.35)	
Unknown	11/13	9/24	0.15 (0.05–0.48)	
Age at randomization				0.04
<70 yr	361/596	165/603	0.26 (0.22–0.32)	
≥70 yr	174/361	83/357	0.36 (0.28–0.47)	
WHO performance status				0.25
0	402/744	190/745	0.30 (0.25–0.36)	
1 or 2	133/213	58/215	0.25 (0.18–0.34)	
NSAID or aspirin use				0.29
No	394/718	179/714	0.27 (0.23–0.32)	
Yes	141/239	69/246	0.33 (0.25–0.45)	
Radiotherapy planned				0.02
No	425/561	224/564	0.31 (0.26–0.36)	
Yes	110/396	24/396	0.18 (0.12–0.28)	
Recurrent disease				0.49
No	514/919	233/900	0.29 (0.25–0.34)	
Yes	21/38	15/60	0.32 (0.16–0.65)	
Time period				0.34
ABCEG	214/328	110/330	0.33 (0.26–0.41)	
ABCEGH	31/49	12/47	0.21 (0.11–0.43)	
AGH	290/580	126/583	0.27 (0.22–0.34)	
Overall			0.29 (0.25–0.34)	

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Figure 2 (facing page). Forest Plots of Treatment Effect on Overall and Failure-free Survival within Subgroups According to Stratification Factors at Randomization.

In each panel, the dashed vertical line is the point estimate of the hazard ratio for the analysis. Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis. The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability. Time period was defined by corecruiting group; ABCEG corresponds to November 2011 through January 2013, ABCEGH January 2013 through March 2013, and AGH April 2013 through January 2014. NSAID denotes nonsteroidal anti-inflammatory drug.

Table 2. Worst Adverse-Event Grade Reported during Entire Time in the Trial.*

Variable	ADT Alone	Combination Therapy
Safety population		
No. of patients	960	948
Patients with an adverse event — no. (%)		
Any grade	950 (99)	943 (99)
Grade 3–5	315 (33)	443 (47)
Grade 5 only†	3 (<1)	9 (1)
Grade 3–5 adverse events — no. (%)		
Endocrine disorders‡	133 (14)	129 (14)
Cardiovascular disorders	41 (4)	92 (10)
Hypertension	13 (1)	44 (5)
Myocardial infarction	9 (1)	10 (1)
Cardiac dysrhythmia	2 (<1)	14 (1)
Musculoskeletal disorders	46 (5)	68 (7)
Gastrointestinal disorders	40 (4)	49 (5)
Hepatic disorders	12 (1)	70 (7)
Increased ALT level	4 (<1)	53 (6)
Increased AST level	2 (<1)	10 (1)
General disorders	29 (3)	45 (5)
Fatigue	15 (2)	21 (2)
Edema	0	5 (1)
Respiratory disorders	23 (2)	44 (5)
Dyspnea	7 (1)	18 (2)
Laboratory abnormalities	21 (2)	34 (4)
Hypokalemia	3 (<1)	12 (1)
Intention-to-treat population		
Total no. of patients	957	960
No. of patients in safety analysis	953	955
Patients with an adverse event — no. (%)		
Any grade	943 (99)	950 (99)
Grade 3–5	312 (33)	446 (47)
Grade 5 only†	3 (<1)	9 (1)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† In the ADT-alone group, there were two events of myocardial infarction and one event of bronchopneumonia. In the combination group, there were two events of pneumonia (one including sepsis), two events of stroke, and one event each of dyspnea, lower respiratory tract infection, liver failure, pulmonary hemorrhage, and chest infection.
‡ Endocrine disorders included hot flashes and impotence.

of death from coexisting conditions and a relatively shorter follow-up among older men, because a higher proportion were recruited later, after recruitment to the docetaxel comparison in the protocol was completed. Results for failure-free, progression-free, and prostate cancer–specific survival showed a benefit of abiraterone in men regardless of age. Further exploration is possible in a preplanned meta-analysis with two other trials investigating the addition of abiraterone to standard ADT with overlapping patient inclusions: LATITUDE (to be published on June 4, 2017, at NEJM.org)[28] and PEACE1 (ClinicalTrials.gov number, NCT01957436).

The effect size that we report with abiraterone is a little larger with respect to overall survival and substantially larger with respect to failure-free survival than the effect size that we reported with the addition of docetaxel in a similar patient group. The trial results raise the question of what should be regarded as the contemporary standard of care. Abiraterone has a better side-effect profile than docetaxel and is an easier treatment to administer logistically. Conversely, the treatment duration is longer, some patients have long-term effects of glucocorticoid use, and cost is a consideration. In the absence of comparative data, patient choice and the ability of health care systems to support the use of these drugs will determine the relative use of docetaxel and abiraterone.

Perhaps a more important question is whether the benefits of docetaxel and abiraterone can be combined. Although docetaxel may work in part by targeting the androgen-receptor pathway,[29] it generally has a different mechanism of action than abiraterone, and abiraterone is active after docetaxel use.[5] Thus, there may be an additive effect of giving abiraterone immediately after docetaxel in prostate cancer not previously treated with hormone therapy. Some future information will emerge from the STAMPEDE trial, which

A ADT Alone

No. of Patients (no. of patients reporting treatment after progression)								
Any	535	(441)	70	(20)	38	(7)	28	(4)	23
Docetaxel	535	(102)	374	(51)	271	(25)	197	(12)	145
Abiraterone	535	(38)	434	(43)	331	(18)	247	(16)	162
Enzalutamide	535	(24)	448	(52)	331	(35)	229	(15)	165

B Combination Therapy
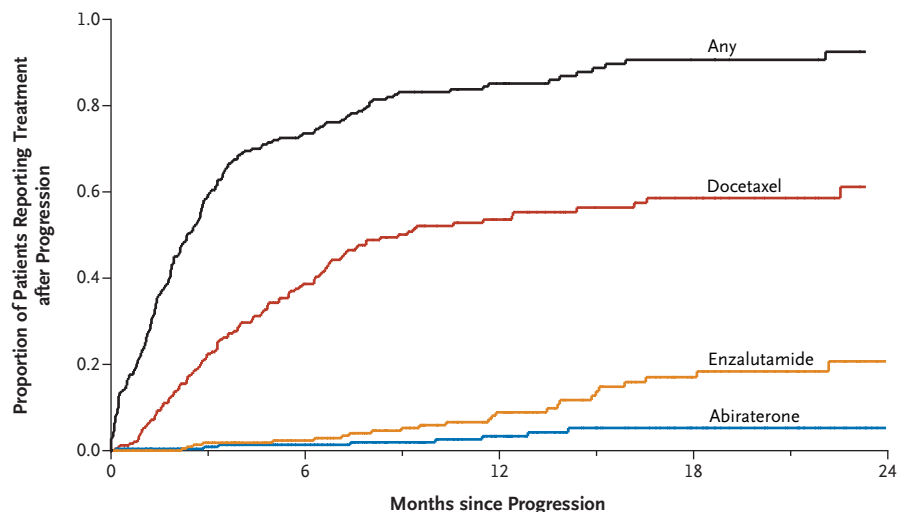
No. of Patients (no. of patients reporting treatment after progression)								
Any	248	(168)	51	(21)	21	(6)	9	(1)	2
Docetaxel	248	(83)	110	(25)	58	(5)	32	(1)	13
Abiraterone	248	(3)	179	(3)	122	(2)	71	(0)	32
Enzalutamide	248	(5)	179	(10)	116	(8)	62	(2)	25

Figure 3. Time until the Initiation of Second-Line Treatment after First Event of Radiologic, Clinical, or PSA Progression.

includes a further comparison involving abiraterone plus enzalutamide in which docetaxel was permitted as part of the standard of care in patients who had undergone randomization start-ing in 2016. The PEACE1 trial also now includes patients receiving docetaxel as part of the standard of care and will help address the question of whether the benefits seen with docetaxel[15-17]

are overlapping or additional to those seen with abiraterone.

Finally, the design used in the trial has allowed the STAMPEDE investigators to address multiple questions within a single trial platform, making efficient use of control-group patients.[22] The current abiraterone comparison eventually recruited 1917 patients in 2 years 3 months, well ahead of target and underlining the power of this design to address multiple questions efficiently and rapidly. There are three further randomizations within the trial that will yield survival results in the coming years, which means that a single protocol will have answered at least 10 different primary questions in 15 years; two further comparisons are also in the late stages of planning. To address as many questions in separate trials would have taken considerably longer and required far more control-group patients.

In conclusion, men with locally advanced or metastatic prostate cancer who received ADT plus abiraterone and prednisolone had significantly higher rates of overall and failure-free survival than those who received ADT alone. In addition, combination therapy was associated with fewer symptomatic skeletal events.

APPENDIX

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