## Europe PMC Funders Group Author Manuscript *N Engl J Med.* Author manuscript; available in PMC 2018 January 27.

Published in final edited form as: *N Engl J Med.* 2017 July 27; 377(4): 338–351. doi:10.1056/NEJMoa1702900.

## 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

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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.)

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 design12–14 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 trials17–19 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 investivestigating 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 coauthors. 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 (combination 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 ADTalone 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 hazards (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, Fig. 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 attributed 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 cancerspecific 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 ADTalone 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 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 data15,16,24–27 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 adverseevent 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 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 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 starting 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 docetaxel15–17 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

Supported by Cancer Research U.K., Medical Research Council, Astellas Pharma, Clovis Oncology, Janssen, Novartis, Pfizer, and Sanofi Aventis.

## Appendix

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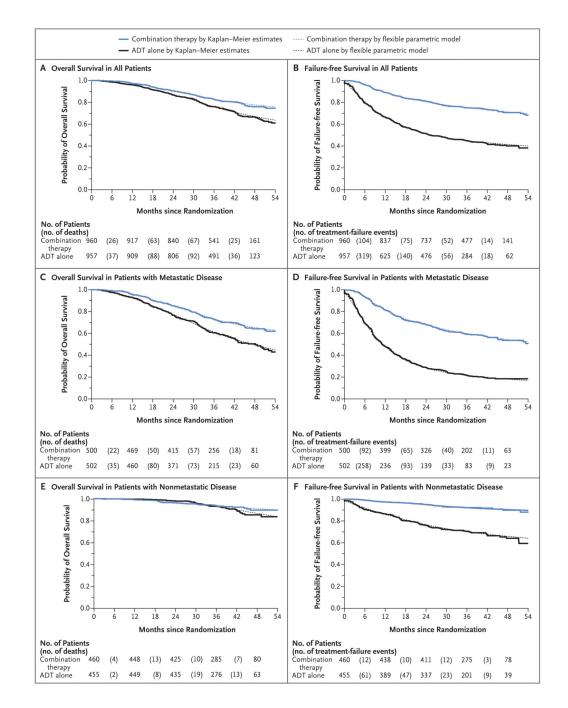
Brighton and Sussex University Hospitals NHS Trust (F.M.) and Sussex Cancer Centre, Royal Sussex County Hospital (A.R.), Brighton, NHS Highland, Inverness (N.M.), Royal Surrey County Hospital, Guildford (J.M.-K.), Northern Ireland Cancer and Queens University, Belfast (J.O.), Lancashire Teaching Hospitals NHS Trust, Preston (O.P.), Churchill Hospital, Oxford (A.P.), Shrewsbury and Telford Hospitals NHS Trust, Shrewsbury (N.N.S.), East Kent Hospitals NHS Trust, Canterbury (C.T.), Swansea University College of Medicine, Swansea (J. Wagstaff), and Christie NHS Foundation Trust, Manchester (J. Wylie) — all in the United Kingdom; and the Department of Medical Oncology, Kantonsspital St. Gallen, St. Gallen (S.G.), and University Hospital of Lausanne, Lausanne (D.R.B.) — both in Switzerland. Two of the authors (D.M., R.M.) were unaffiliated lay members of the STAMPEDE investigators.

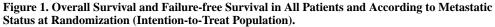
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Combination therapy was androgen-deprivation therapy (ADT) plus abiraterone acetate and prednisolone. Treatment failure was defined as radiologic, clinical, or prostate-specific antigen (PSA) progression or death from prostate cancer.

Subgroup         ADT Alone         Therapy         (95% Cl)           no. of treatment-failure events/no. of patients         Inc. of patients         Inc. of patients           Metastatic status         142/455         38/460         Inc. of treatment-failure events/no. of patients           Metastatic status         142/455         38/460         Inc. of treatment-failure events/no. of patients           Metastatic status         393/502         210/500         Inc. of treatment-failure events/no. of patients           Nodal status         Inc. of treatment-failure events/no. of patients         Inc. of treatment-failure events/no. of patients           Nodal status         Inc. of treatment-failure events/no. of patients         Inc. of patients           Negative         184/438         69/434         Inc. of treatment-failure events/no. of patients           Nodal status         120/1484         Inc. of treatment-failure events/no. of patients         Inc. of treatment-failure events/no. of patients           Status         131/13         199/715         Inc. of treatment-failure events/no. of patients         Inc. of treatment-failure events/no. of patients           Inc. of yr         361/596         165/603         Inc. of treatment-failure events/no. of patients         Inc. of treatment-failure events/no. of patients           No         394/718         179/714         Inc. of treatment-fa	Survival Combination Hazard Ratio with Combination Therapy ADT Alone Therapy (95% CI)	P Value for Interaction
Nonnetastatic 44/455 34/460 Nodal status 83/438 61/434 Positive 16/4/483 113/484 Positive 16/4/483 113/484 Positive 16/4/483 113/484 Positive 16/4/483 113/484 Positive 16/4/483 113/484 Positive 16/4/88 113/484 Positive 12/6/721 14/715 Subroom 6,13 7/24 Subroom 6,13 7/24 WHO performance status 0 No 216/721 14/715 Na or 2 80/213 47/215 Na or 2 80/210 12 14 Combination Therapy Better ADT Alon Hazard Ratio with Combinat 95% CI) Postive 32/483 16/0/484 Positive 32/483 10/424 Positive 32/483 16/0/484 Positive 32/483 16/0/484 Positi		
Metastatic       218/502       150/500         Negative       83/438       61/434         Negative       13/434	status	0.37
Nodal status Negative Negative 164,433 113/484 Positive 164,433 113/48 10/42 164 Positive 164,433 160,444 Positive 164,433 160,434 Positive 164,434 164,434 Positive 164	astatic 44/455 34/460 0.75 (0.48–1.18	3)
Negative         83/438         61/434           Positive         16/4/433         113/484           Indeterminate         15/36         10/42           s7         40/223         33/221           s7         40/233         37/24           ge at randomization         5/70 r         180/596           s70 r         180/596         10/603           s70 r         180/214         137/745           1 or 2         80/213         47/215           No         10/718         132/714           Yes         71/239         52/246           Rediotherapy planned         10/35         26/396           No         26/591         160/564         40           No         26/591         10/47         40/47           ABCE G         122/128         9/330         40           ABCE G         122/128         50/500         40/4         05         06 07 0.5 0.7 0.5 0.2 10 <td>tic 218/502 150/500</td> <td>5)</td>	tic 218/502 150/500	5)
Positive 164/433 113/484 Indeterminate 15/36 10/42 Gleason score 40/223 33/221 8-10 216/721 144/715 Whto performance status 0 126/721 144/715 0 216/721 144/715 0 2182/744 137/745 0 2182/744 137/745 0 219/745 0 219/74 745 36/396 24/396 Recurrent disease 254/919 171/900 748 256/51 160/564 0 4 05 0.6 07 0.8 09 10 12 14 Combination Therapy Better ADT Alone 740 4 05 0.6 0.7 0.8 09 10 12 14 Combination Therapy Better ADT Alone 127/749 10/47 ACH 123/780 79/583 Overall 423/84 160/484 0 0 417/721 199/715 0 0 425/561 19/22 40/221 40/221 40/221 40/221 40/221 40/221 40/221 40/221 40/224 40/244 40/2	us	0.80
Positive 164,433 113/484 Indeterminate 15/36 10/42 Gleason score 57 8-10 216/721 144/715 	e 83/438 61/434 0.69 (0.49-0.90	5)
Indeterminate I5/36 I0/42 S (Gason score 40/223 33/221 S	164/483 113/484	7)
Gleason score s7 40/223 33/221 8-10 216/721 144/715 Unknown 6,713 77/45 C70 yr 82/361 10/603 a70 yr 82/361 10/603 a70 yr 82/361 174/357 WHO performance status 0 182/744 137/745 1 or 2 80/213 47/215 NSAID or aspirin use No 226/561 160/564 Wes 8/38 13/60 Time period ABCEG 122/328 95/330 ABCEG 124/348 10/330 ABCEG 124/328 110/330 ABCEG 124/328	ninate 15/36 10/42 • 0.68 (0.29–1.5)	7)
8-10 Unknown 6/13 7/24 Age at randomization Age at randomization 6/13 7/24 ***   Age at randomization 180/596 110/603 ***   0 182/744 ***   0 182/744 ***   1 or 2 80/213 8/7/215 ***   NSAID or aspirin use No 191/718 122/714 ***   NSAID or aspirin use No 226/561 160/564 ***   No 226/561 160/564 ***   No 226/561 160/564 ***   No 226/561 160/564 ***   No 226/919 171/900 ***   Yes 8/38 13/60 ***   Time period ABCEG 122/328 123/580 ***   ACH 123/580 ***   ACH 123/580 ***   Yes 8/38 13/60 ***   Failure-free Survival Subgroup ADT Alone ADT Recent Fielling ***   Metastatic Nonmetastic Nonretastic Nodal status ***   Nonretastic ***   107/223 ***   Metastatic ***   107/223 ***   ***	tore	0.57
8-10       216/721       144/715         Ownown       6/13       7/24         Age at randomization       5/13       7/24         <70 yr	40/223 33/221 0.76 (0.48–1.23	3)
Unknown 6/13 7/24	216/721 144/715 0.59 (0.48–0.73	3)
Age at randomization <pre></pre>		ú
<70 yr	domization	0.003
z70 yr       82/361       74/357         WHO performance status       182/744       137/745         0 ar 2       80/213       47/215         NSAID or aspirin use       191/718       132/714         Yes       71/239       52/246         Radiotherapy planned       226/561       160/564         No       226/561       160/564         Yes       8/38       13/60         Time period       8/38       13/60         ABCEG       122/128       95/330         ABCEG       122/3580       79/583         Overall       Otad       0.5 0.6 0.7 0.8 0.9 1.0 1.2 1.4         Combination       Therapy       ADT Alone         Therapy       ADT Alone       Therapy         Metastatic status       142/455       38/460         Non of treatment-foilure events/no. of patients       4DT Alone         Metastatic 142/455       38/460	180/596 110/603 0.51 (0.40-0.65	
WHO performance status       1 <td></td> <td></td>		
0 182/744 137/745 1 or 2 80/213 47/215 NSAID or aspirin use No 191/718 132/714 Yes 71/239 52/246 Recurrent disease No 226/561 160/564 No 226/561 160/564 No 254/919 171/900 Yes 8/38 13/60 Time period ABCEG 122/328 95/330 ABCEG 122/328 95/330 ABCEG 122/328 95/330 ABCEG 122/328 95/330 ACH 123/580 79/583 Overall Failure-free Survival Combination Therapy Better ADT Alon Therapy no. of treatment-failure events/no. of patients Metastatic 339/502 210/500 Nodal status Negative 184/438 69/434 Positive 325/483 160/484 Indeterminate 28/36 19/42 Gleason score s7 107/223 40/221 s70 yr 361/596 165/603 s70 yr 17/136 183/357 WHO performance status 0 402/744 190/745 1 or 2 139/213 58/215 NSAID or aspirin use NSAID or aspirin	ormance status	0.11
l or 2 80/213 47/215 NAD or aspirin use No 191/718 132/714 Yes 71/239 52/246 Radiotherapy planned No 256/919 171/900 Yes 36/396 24/396 Recurrent disease No 256/919 171/900 Yes 8/313 13/60 Time period ABCEG 122/328 95/330 ABCEG 122/328 95/330 ABCEG 122/328 95/330 ABCEG 122/328 79/583 Overall Failure-free Survival Subgroup ADT Alone No of treatment-foilure events/no. of patients Metastatic status Nonmetastic 142/455 38/460 Metastatic 393/502 210/500 Nodal status 393/502 210/500 Nedal status 323/483 160/484 Indeterminate 28/36 19/42 Safe 10/223 Safe 10/224 Safe 10	182/744 137/745 0.69 (0.56–0.8)	
NSAID or aspirin use 19/718 132/714 Yes 71/239 52/246 Radiotherapy planned No 226/561 160/564 Yes 36/396 24/396 Recurrent disease No 254/919 171/900 Yes 8/38 13/60 Time period ABCEG 122/328 95/330 ABCEG 124/328 100/348 ABCEG 124/328 100/346 No 425/561 224/564 No 425/561 224/564 No 425/561 224/564 No 425/561 224/564 No 425/561 224/564 No 425/561 224/564 No 425/561 224/36 ABCEG 214/328 110/330 ABCEG 124/328 110/330	80/213 47/215 0.50 (0.35-0.72	2)
No       191/718       132/714         Yes       71/239       52/246         Radiotherapy planned       26/561       160/564         Yes       8/38       13/60         Time period       8/38       13/60         ABCEG       122/580       95/330         ABCEG       122/580       79/583         Overall       Image: Combination Therapy Better       ADT Alone Therapy no. of treatment-failure events/no. of patients         Metastatic Status       102/152       210/500       Image: Combination Therapy Better       ADT Alone ADT Alone Therapy no. of treatment-failure events/no. of patients         Metastatic Status       142/455       38/460       Image: Combination Therapy Positive       Image: Combination Therapy Positive         Solgroup       ADT Alone Therapy Positive       184/438       69/434       Image: Combination Positive         Solgroup       184/438       19/42       Image: Combination Positive       Image: Combination Positive         Solgroup       184/438       69/434       Image: Combination Positive       Image: Combination Positive         Solgroup       184/438       69/434       Image: Combination Positive       Image: Combination Positive         Solgroup       184/138       160/484       Image: Combination Positive <t< td=""><td></td><td>0.35</td></t<>		0.35
Yes       71/239       52/246         No       226/561       160/564         Yes       36/396       24/396         Recurrent disease       171/900		
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No         226/561         160/564           Yes         36/396         24/396           Recurrent disease         25/9/91         171/900           No         25/9/91         171/900           Tres period         8/38         13/60           ABCEG         122/328         95/330           ABCEG         122/328         95/330           ABCEG         122/328         95/330           ABCEG         122/328         97/583           Overall	11/257 52/240 0.71 (0.50-1.02	
Yes       36/396       24/396         Recurrent disease       254/919       171/900         No       254/919       171/900         Yes       8/38       13/60         Time period       ABCEG       122/328       95/330         ABCEG       122/328       95/330	226/561 160/564 • 0.63 (0.51–0.77	0.89
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No         254/919         171/900           Yes         8/38         13/60           Time period         ABCEG         122/328         95/330           ABCEG         122/328         95/330         ABCEG           ABCEG         123/580         79/583         ABCEG           Overall         Combination         Hazard Ratio with Combination           Failure-free Survival         Combination         Hazard Ratio with Combination           Stobgroup         ADT Alone         Therapy         Hazard Ratio with Combination           Metastatic         142/455         38/460         Hazard Ratio with Combination           Nonmetastic         142/455         38/460         Hazard Ratio with Combination           Negative         184/438         69/434         Hazard Ratio with Combination           Negative         184/438         19/42         Hazard Ratio with Combination           Scason score         23/483         160/484         Heterminate           Indeterminate         28/36         19/42         Heterminate           Sr         0         402/744         190/715         Heterminate           Or 2         103/213         58/215         Heterminate         Heterminate           <	36/396 24/396 0.64 (0.38–1.02	
Yes       8/38       13/60         Time period       ABCEG       122/328       95/330         ABCEG       122/328       95/330		0.19
Time period ABCEG 122/328 95/330 ABCEGH 17/49 10/47 AGH 123/580 79/583 Overall Failure-free Survival Combination Failure-free Survival Combination Combination ADT Alone Therapy no. of treatment-failure events/no. of patients Metastatic 393/502 210/500 Nodal status Nonmetastatic 142/455 38/460 Metastatic 393/502 210/500 Nodal status Nometastatic 393/502 210/500 Nodal status Nometastatic 393/502 210/500 Nodal status Nometastatic 393/502 210/500 Nodal status Sale 19/42 Gleason score s <sup>7</sup> 107/223 40/221 8-10 417/721 199/715 Unknown 11/13 9/24 40/2744 190/745 - s70 yr 361/596 165/603 s70 yr 361/596 170 yr 36/50 s70 yr 361/596 170 yr 36/50 s70 yr 361/596 170 yr 36/50 s70 yr 360 yr 36/50 s70 y		
ABCEG       122/328       95/330         AGH       17/49       10/47         AGH       123/580       79/583         Overall       04       05       06       07       08       12       14         Combination       Therapy       ADT Alone       Therapy       Hazard Ratio with Combination         Failure-free Survival       Combination       Hazard Ratio with Combination       142/455       38/460         Metastatic       132/2483       160/484       —       —       —       —         Nometastatic       132/2483       160/484       —       —       —       —       —         Segary       184/438       69/434       —       …	8/38 13/60 0.94 (0.35-2.52	
ABCECH       17/49       10/47         AGH       123/580       79/583         Overall       04       05       06       07       08       09       10       12       14         Combination         Failure-free Survival       Combination         Hazard Ratio with Combinat (95% CI)         Non- of treatment-failure events/no. of patients         Metastatic       393/502       210/500		0.62
AGH 123/580 79/583 Overall  Coverall  Combination  Failure-free Survival ADT Alone  Therapy no. of treatment-failure events/no. of patients  Metastatic 142/455 38/460 Metastatic 142/455 38/460 Metastatic 393/502 210/500 Nodal status Nonmetastatic 393/502 210/500 Nodal status Nongative 184/438 69/434  Select and monitation  Solver and the select and	122/328 95/330 0.69 (0.53-0.90	D)
Overall <ul> <li>Out</li> <li>Out</li></ul>		
Failure-free Survival         Combination Therapy no. of treatment-failure events/no. of patients         Hazard Ratio with Combinat (95% Cl)           Metastatic stats         142/455         38/460           Nonmetastatic         142/455         38/460           Metastatic status         393/502         210/500           Nodal status         160/484	123/580 79/583 0.59 (0.44-0.78	3)
Failure-free Survival         Combination Therapy no. of treatment-failure events/no. of patients         Hazard Ratio with Combinat (95% Cl)           Metastatic stats         142/455         38/460           Nonmetastatic         142/455         38/460           Metastatic status         393/502         210/500           Nodal status         160/484		
Failure-free Survival Subgroup     Combination ADT Alone     Hazard Ratio with Combinat (95% Cl)       no. of treatment-failure events/no. of patients     Hazard Ratio with Combinat (95% Cl)       Metastatic status     393/502       Normetastatic     142/455       393/502     210/500       Negative     184/438       Positive     323/483       160/484	0.63 (0.52–0.76	5)
no. of treatment-failure events/no. of patients       Vetastatic status       Nonmetastatic     142/455     38/460       Metastatic     393/502     210/500       Nodal status     393/502     210/500       Negative     184/438     69/434       Positive     323/483     160/484       Indeterminate     28/36     19/42       Sr     107/223     40/221       #     -     -       Sr     107/223     40/221       #     -     -       Sr     10/7/721     199/715       Unknown     11/13     9/24       #     -     -       Yor     361/596     165/603       >70 yr     313/213     58/215       No     402/744     190/745       1 or 2     133/213     58/215       No     394/718     179/714       Yes     10/396     24/336       Recurrent disease     -     -       No     514/919     23/900       Yes     11/49	combination mature with combination metapy	P Value f
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Nonmetastatic       142/455       38/460         Metastatic       393/502       210/500         Nodal status       9/434       9/42         Negative       184/438       69/434         Positive       323/483       160/484         Indeterminate       28/36       19/42         Gleason score       27       107/223       40/221         &= 10       417/721       199/715       9/44         Age at randomization       270 yr       361/596       165/603         > 70 yr       361/596       165/603       270 yr         > 10 4/17/721       199/715       9/24         WHO performance status       0       402/744       190/745         0       402/744       190/745       9/24         No       394/718       179/714       9/24         Yes       141/239       69/246       9/246         Radiotherapy planned       9/216       9/246       9/246         No       324/919       233/900       9/24       9/24         Yes       10/396       24/396       9/24       9/24         Recurrent disease       9/218       15/60       9/24       9/24         No		Interactio
Metastatic       393/502       210/500         Nodal status       393/502       210/500         Negative       184/438       69/434         Positive       323/483       160/484         Indeterminate       28/36       19/42         Gleason score       37       107/223       40/221         \$       \$       10/721       199/715         Unknown       11/13       9/24       \$         \$       \$       70 yr       361/596       165/603         \$       70 yr       361/596       165/603         \$       70 yr       174/361       83/357         WHO performance status       0       402/744       190/745         1 or 2       133/213       58/215       -         NSAID or aspirin use       58/215       -       -         No       394/718       179/714       -       -         Yes       110/396       24/396       -       -         Recurrent disease       No       514/919       233/900       -       -         No       514/919       233/900       -       -       -         Yes       110/396       21/38       15/60		
Nodal status     10/10     10/10       Negative     184/438     69/434       Positive     323/483     160/484       Indeterminate     28/36     19/42       Gleason score     57     107/223     40/221       \$\$^7     107/1223     40/221       \$\$^7     107/1223     40/221       \$\$^7     107/1223     40/221       \$\$^70 yr     361/596     165/603       \$\$^70 yr     361/596     165/603       \$\$^70 yr     361/596     165/603       \$\$^70 yr     361/596     165/603       \$\$^70 yr     174/361     83/357       WHO performance status     90/745       0     402/744     190/745       1 or 2     133/213     58/215       NSAID or aspirin use     No       No     394/718     179/714       Yes     19/246       Radiotherapy planned     10/396       No     425/561     224/396       Recurrent disease     76/80       No     514/919     233/900       Yes     21/38     15/60       Time period     110/330     -       ABCEG     21/32     110/330       ABCEGH     31/49     12/47       AGCH	status	0.08
Negative     184/438     69/434       Positive     323/483     160/484       Indeterminate     28/36     19/42       ST     10/223     40/221       \$\$^7\$     107/223     40/221       \$\$^1\$     11/13     9/24       Age at randomization     11/13     9/24       \$\$^70\$ yr     361/596     165/603       \$\$^70\$ yr     174/361     83/357       WHO performance status     0     402/744       0     402/744     190/745       1 or 2     133/213     58/215       NSAID or aspirin use     10/306     24/396       No     39/4/718     179/714       Yes     110/396     24/396       Recurrent disease	status astatic 142/455 38/460 0.21 (0.15-0.31	0.08
Positive     323/483     160/484       Indeterminate     28/36     19/42       Gleason score	status astatic 142/455 38/460 0.21 (0.15-0.3) tic 393/502 210/500 0.31 (0.26-0.3)	0.08 1) 7)
Indeterminate         22/36         19/42           Gleason score         28/36         19/42           s-7         107/223         40/221           8-10         417/721         199/715           Unknown         11/13         9/24           Age at randomization         11/13         9/24           <70 yr	status astatic 142/455 38/460 0.21 (0.15-0.3) tic 393/502 210/500 0.31 (0.26-0.3) us	0.08 1) 7) 0.35
Gleason score 10/10 10/10 ≤7 107/223 40/221 S=7 107/223 40/221 Unknown 417/721 199/715 Unknown 11/13 9/24 <70 yr 361/596 165/603 ≥70 yr 361/596 165/603 ≥70 yr 361/596 165/603 ≥70 yr 361/596 165/603 ≥70 yr 361/596 165/603 ⇒70 yr 361/596 165/60 ⇒70 yr 361/596 165/596 165/596 165/596 165/596 165/596	status         0.21 (0.15-0.3)           astatic         142/455         38/460         0.21 (0.15-0.3)           tic         393/502         210/500         0.31 (0.26-0.3)           us         0.26 (0.20-0.33)         0.26 (0.20-0.33)	0.08 1) 7) 0.35 5)
≤7       107/223       40/221         8-10       417/721       199/715         Unknown       11/13       9/24         Age at randomization          <70 yr	status         0.21 (0.15-0.3)           astatic         142/455         38/460         0.21 (0.15-0.3)           tic         393/502         210/500         0.31 (0.26-0.3)           us         184/438         69/434         0.26 (0.20-0.3)           323/483         160/484         0.29 (0.24-0.3)	0.08 1) 7) 5)
8-10       417/721       199/715         Unknown       11/13       9/24         Age at randomization	status astatic 142/455 38/460 0.21 (0.15-0.31 tic 393/502 210/500 0.31 (0.26-0.32 us 0.26 (0.20-0.32 323/483 160/484 0.29 0.24 0.03 ninate 28/36 19/42 0.44 (0.24-0.88	0.08 1) 7) 0.35 5) 5)
Unknown 11/13 9/24 Age at randomization            420 yr         361/596         165/603           >70 yr         174/361         83/357           WHO performance status         0         402/744         190/745           0 o         402/744         190/745	status         0.21 (0.15-0.3)           astatic         142/455         38/460         0.21 (0.15-0.3)           tic         393/502         210/500         0.31 (0.26-0.3)           us         0.26 (0.20-0.3)         0.29 (0.24-0.34)           astatic         123/483         160/484         0.29 (0.24-0.34)           ninate         28/36         19/42         0.44 (0.24-0.86)	0.08 1) 7) 0.35 5) 5) 0) 0.73
Onknown       11/13       9/24         ge at randomization	status         astatic         142/455         38/460         0.21 (0.15-0.3]           astatic         393/502         210/500         0.31 (0.26-0.3)           us         184/438         69/434         0.26 (0.20-0.3)           astatic         28/36         19/42         0.29 (0.24-0.3)           core         107/223         40/221         0.26 (0.18-0.3)	0.08 1) 7) 0.35 5) 5) 0) 0.73 8)
<70 yr	status         0.21 (0.15-0.3)           astatic         142/455         38/460         0.21 (0.15-0.3)           us         0.31 (0.26-0.3)         0.31 (0.26-0.3)           us         323/483         160/484         0.29 (0.24-0.3)           ninate         28/36         19/42         0.44 (0.24-0.8)           tore         107/223         40/221         0.29 (0.15-0.3)	0.08 1) 7) 0.35 5) 5) 0.73 8) 5)
270 yr       174'j361       83'j357         WHO performance status       402/744       190/745         0       402/744       190/745         1 or 2       133/213       58/215         NSAID or aspirin use       9/213       58/215         No       394/718       179/714         No       425/561       224/564         Yes       110/396       24/396         Rediotherapy planned       10/396       24/396         No       425/561       224/564         Yes       10/396       24/396         Recurrent disease       10/396       24/396         No       514/919       233/900         Yes       21/38       15/60         Time period       48CEG       214/328         ABCEG       214/328       10/330         ABCEGH       31/49       12/47         AGH       290/580       126/583	status     0.21 (0.15-0.3)       astatic     142/455     38/460       tic     393/502     210/500       us     0.31 (0.26-0.3)       us     0.26 (0.20-0.3)       astatic     142/455       astatic     142/455       astatic     142/455       us     0.31 (0.26-0.3)       us     0.26 (0.20-0.3)       astatic     0.29 (0.24-0.3)       astatic     107/223       us     0.26 (0.18-0.3)       us     0.29 (0.24-0.3)       us     0.29 (0.25-0.3)       us     0.29 (0.25-0.3)       us     0.11 (1.3 9)/24	0.08 1) 7) 0.35 5) 5) 0.73 8) 0.73
WHO performance status     0     402/744     190/745       0     402/744     190/745       1 or 2     133/213     58/215       NSAID or aspirin use     394/718     179/714       Yes     141/239     69/246       Radiotherapy planned     425/561     224/564       No     425/561     224/564       Yes     110/396     24/336       Recurrent disease     7       No     514/919     233/900       Yes     21/38     15/60       Time period     110/330     48CEG       ABCEG     214/328     110/330       ABCEG     214/328     110/340       ABCEG     290/580     126/583	status     0.21 (0.15-0.3)       astatic     142/455     38/460       astatic     393/502     210/500       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       323/483     160/484       323/483     160/484       0.27 (0.24-0.3)     0.29 (0.24-0.3)       core     107/223     40/221       107/721     199/715     0.29 (0.25-0.3)       n     11/13     9/24	0.08 1) 0.35 5) 5) 0) 0.73 8) 5) 3) 0.04
0 402/744 190/745	status	0.08 1) 7) 0.35 5) 0) 0.73 8) 0.73 8) 0.04
l or 2 133/213 58/215 NSAID or aspirin use No 394/718 179/714 Yes 141/239 69/246 Radiotherapy planned No 425/561 224/564 Yes 110/396 24/396 Recurrent disease No 514/919 233/900 Yes 21/38 15/60 Time period ABCEG 214/328 110/330 ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status       0.21 (0.15-0.3)         astatic       142/455       38/460         tic       393/502       210/500         us       0.31 (0.26-0.3)         e       184/438       69/434         323/483       160/484       0.29 (0.24-0.3)         orre       107/223       40/221         m       11/13       9/24         domization       361/596       165/603         174/361       83/357       0.26 (0.22-0.3)	0.08 1) 7) 0.35 5) 0.73 8) 0.73 8) 0.04 2) 7)
NSAID or aspirin use 01/00 01/01 01/	status     0.21 (0.15-0.3)       astatic     142/455     38/460       astatic     142/455     38/460       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       323/483     160/484       323/483     160/484       0.26 (0.20-0.3)       ninate     28/36       107/223     40/221       m     11/13       9/24     0.26 (0.18-0.3)       domization     0.26 (0.25-0.3)       361/596     165/603       174/361     83/357	0.08 1) 7) 0.35 5) 0) 0.73 3) 5) 0 0.73 3) 0.73 2) 0.04 2) 0.25
No         394/718         179/714           Yes         141/239         69/246           Radiotherapy planned         69/246           No         425/561         224/564           Yes         10/396         24/396           Recurrent disease         10/396         24/396           No         514/919         233/900           Yes         21/38         15/60           Time period         ABCEG         214/328           ABCEGH         31/49         12/47           AGH         290/580         126/583	status     0.21 (0.15-0.3)       astatic     142/455     38/460       usatatic     142/455     38/460       us     0.21 (0.15-0.3)       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       us     0.29 (0.24-0.3)       other     0.29 (0.25-0.3)       other     0.29 (0.25-0.3)       other     0.29 (0.25-0.3)       other     0.29 (0.25-0.3)       other     0.15 (0.05-0.48)       domization     0.15 (0.05-0.48)       ormance status     402/744       402/744     190/745	0.08 0.35
Yes         141/239         69/246           Radiotherapy planned	status     0.21 (0.15-0.3)       astatic     142/455     38/460       astatic     142/455     38/460       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       323/483     160/484       323/483     160/484       0.26 (0.20-0.3)       0.27 (0.15-0.3)       0.27 (0.15-0.3)       0.28 (0.20-0.3)       0.29 (0.24-0.3)       0.29 (0.25-0.3)       0.20 (0.26-0.3)       0.20 (0.26-0.3)	0.08 () () () () () () () () () ()
Radiotherapy planned     111/253     60/210       No     425/561     224/564       Yes     110/396     24/396       Recurrent disease     10/396	status     0.21 (0.15-0.3)       astatic     142/455     38/460     0.21 (0.15-0.3)       us     0.21 (0.15-0.3)     0.21 (0.26-0.3)       us     0.26 (0.20-0.3)     0.29 (0.24-0.3)       astatic     142/455     19/42     0.26 (0.20-0.3)       ininate     28/36     19/42     0.29 (0.24-0.3)       ininate     28/36     19/42     0.26 (0.18-0.3)       ininate     107/223     40/221     0.26 (0.18-0.3)       ininate     11/13     9/24     0.26 (0.28-0.3)       ininate     361/596     165/603     0.26 (0.22-0.3)       inframe     361/596     165/603     0.26 (0.28-0.4)       inframe     402/744     190/745     0.30 (0.25-0.34)       inframe     402/744     190/745     0.30 (0.25-0.34)       inframe     33/213     58/215     0.25 (0.18-0.34)	0.08 0.35 0.35 0.35 0.35 0.73 0.73 0.73 0.73 0.73 0.73 0.74 0.25 1 0.25 0.29
Radiotherapy planned No 425/561 224/564 Yes 110/396 24/396 No 514/919 233/900 Yes 21/38 15/60 Time period ABCEG 214/328 110/330 ABCEG 214/328 110/330 ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status     0.21 (0.15-0.3)       astatic     142/455     38/460       astatic     393/502     210/500       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       323/483     160/484       323/483     160/484       core     0.7/223       40/721     199/715       ominate     0.26 (0.18-0.3)       0.27 (0.25-0.3)       odmization     0.26 (0.20-0.3)       316/596     165/603       174/361     83/357       0.26 (0.22-0.3)       0.27 (0.25-0.3)       0.28 (0.21-0.3)       0.29 (0.25-0.3)       0.30 (0.25-0.3)       0.30 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.30 (0.25-0.3)       0.26 (0.20-0.3)       0.27 (0.22-0.3)       0.28 (0.21-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.29 (0.25-0.3)       0.20 (0.25-0.3)       0.21 (0.25-0.3)       0.22 (0.25-0.3)       0.23 (0.25-0.3)       0.25 (0.18-0.3)       0.27 (0.22-0.3)       394/718     179/714	0.08 (7) (0.35 (5) (7) (8) (7) (8) (7) (7) (7) (7) (7) (7) (7) (7
Yes         110/396         24/396           No         514/919         233/900           Yes         21/38         15/60           Time period         10/330	status     0.21 (0.15-0.3)       astatic     142/455     38/460     0.21 (0.15-0.3)       us     0.31 (0.26-0.3)       us     0.26 (0.20-0.3)       23/343     160/484     0.29 (0.24-0.3)       ninate     28/36     19/42     0.44 (0.24-0.80)       ore     0.26 (0.18-0.3)     0.29 (0.25-0.3)       ininate     28/36     19/42     0.26 (0.18-0.3)       ininate     28/36     19/15     0.29 (0.25-0.3)       ininate     0.29 (0.25-0.3)     0.29 (0.25-0.3)       ininate     11/13     9/24     0.15 (0.05-0.4)       ininate     361/596     165/603     0.26 (0.22-0.3)       ininate     313/213     58/215     0.36 (0.28-0.4)       ininate     394/718     179/714     0.27 (0.23-0.33)       ininate     394/718     179/714     0.27 (0.23-0.33)	0.08 0.35 0.35 0.35 0.35 0.73 0.74 0.74 0.75
Yes         110/396         24/396           No         514/919         233/900           Yes         21/38         15/60           Time period         10/330	status     0.21 (0.15-0.3)       astatic     142/455     38/460       ustatic     139/502     210/500       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       astatic     141/721       107/223     40/221       us     0.29 (0.24-0.3)       0.29 (0.24-0.3)       ocre     0.29 (0.24-0.3)       107/223     40/221       us     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       0.11/13     9/24     0.15 (0.05-0.48)       domization     361/596     165/603       0rmance status     402/744     190/745       133/213     58/215     0.30 (0.25-0.3)       aspirin use     394/718     179/714       141/239     69/246     0.33 (0.25-0.4)	0.08 (7) (7) (7) (7) (7) (7) (7) (7)
Recurrent disease No 514/919 233/900 Yes 21/38 15/60 Time period ABCEG 214/328 110/330 ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status     0.21 (0.15-0.3)       astatic     142/455     38/460       itic     393/502     210/500       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       323/483     160/484       323/483     160/484       ininate     28/36       107/223     40/221       ininate     0.26 (0.20-0.3)       isore     0.27 (0.25-0.3)       ininate     11/13       9/24     0.50 (0.20-0.3)       isore     0.26 (0.20-0.3)       isore     0.26 (0.20-0.3)       isore     0.26 (0.20-0.3)       0.27 (0.25-0.3)     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       0.29 (0.25-0.3)     0.29 (0.25-0.3)       isore     0.17/21 (199/715       isore     0.36 (0.28-0.3)       isore     0.33 (0.25-0.4)       isore     0.30 (0.25-0.3)       isore     0.32 (0.18-0.3)       isore     0.26 (0.22-0.3)       isore     0.36 (0.28-0.4)       isore     0.32 (0.18-0.4)       isore     0.32 (0.28-0.4)       isore     0.33 (0.25-0.4)       isore     0.30 (0.25-0.4)       isore     0.32 (0.18-0.4)       isore     0.33 (0.25-0.4)	0.08 0.35 0.35 0.35 0.35 0.35 0.35 0.35 0.73 0.74 0.75
Yes         21/38         15/60           Time period         ABCEG         214/328         110/330           ABCEG         214/328         110/330	status     0.21 (0.15-0.3)       astatic     142/455     38/460       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.3)       us     0.29 (0.24-0.3)       astatic     147/721     19/715       us     0.29 (0.25-0.3)       us     0.29 (0.25-0.3)       us     0.29 (0.26-0.3)       us     0.29 (0.26-0.3)       astatic     11/13       107/223     40/221       us     0.29 (0.25-0.3)       us     0.15 (0.05-0.43)       domization     0.26 (0.22-0.3)       us     0.31 (0.26-0.30)       us     133/213     58/215       us     0.31 (0.25-0.36)       uspirin use     394/718     179/714       us     0.31 (0.26-0.36)       uspirin use     391/718       us     0.31 (0.26-0.36)       us     0.31 (0.26-0.43)       uspirin use     0.31 (0.26-0.43)       uspirin use     0.31 (0.26-0.43)       uspirin use	0.08 () () () () () () () () () ()
Yes         21/38         15/60           Time period         ABCEG         214/328         110/330           ABCEG         214/328         110/330         Image: Constraint of the second sec	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.44 (0.24-0.8)         core       107/223       40/221       0.44 (0.24-0.8)         n       11/13       9/24       0.29 (0.25-0.3)         domization       361/596       165/603       0.29 (0.25-0.3)         ormance status       1174/361       83/357       0.36 (0.28-0.3)         ormance status       33/213       58/215       0.29 (0.25-0.3)         aspirin use       33/213       58/215       0.30 (0.25-0.4)         upy planned       141/239       69/246       0.33 (0.25-0.4)         upy planned       141/239       69/246       0.31 (0.26-0.3)         us       0.33 (0.25-0.4)       0.33 (0.25-0.4)       0.33 (0.25-0.4)         us       0.33 (0.25-0.4)       0.33 (0.25-0.4)       0.30 (0.25-0.4)         disease       0.34 (0.24-0.8)       0.33 (0.25-0.4)       0.33 (0.25-0.4)	0.08 7 0.35 5 5 5 0.35 5 0.73 8 0.73 8 0.73 8 0.73 8 0.73 8 0.73 8 0.73 9 0.73 9 0.73 9 0.73 9 0.73 9 0.73 9 0.75 0.25 0.025 0.
Time period ABCEG 214/328 110/330 ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.31 (0.26-0.3)       0.26 (0.20-0.32)         us       323/483       160/484       0.29 (0.24-0.33)         orre       107/223       40/221       0.26 (0.18-0.33)         ininate       28/36       19/42       0.26 (0.20-0.32)         ininate       28/36       19/9/15       0.29 (0.25-0.33)         ininate       11/13       9/24       0.26 (0.22-0.32)         ininate       361/596       165/603       0.26 (0.22-0.32)         ininate       313/213       58/215       0.30 (0.25-0.34)         ininate       394/718       179/714       0.27 (0.23-0.32)         ipp planned       313/213       58/215       0.33 (0.25-0.43)         ipp planned       425/561       224/564       0.31 (0.26-0.34)         ilo(396       24/396       0.31 (0.26-0.34)       0.33 (0.25-0.43)         igease       514/919       233/900	0.08 0.35 0.35 0.35 0.35 0.73 0.74 0.75
ABCEG 214/328 110/330 ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ininate       28/36       19/42       0.26 (0.20-0.3)         core       107/223       40/221       0.29 (0.25-0.3)         ininate       11/13       9/24       0.29 (0.25-0.3)         iomization       361/596       165/603       0.29 (0.25-0.3)         iomization       361/596       165/603       0.36 (0.28-0.4)         iomization       313/213       58/215       0.36 (0.28-0.4)         iaspirin use       394/718       179/714       0.30 (0.25-0.3)         iaspirin use       394/718       179/714       0.33 (0.25-0.4)         iby planned       425/561       224/564       0.31 (0.26-0.3)         idisease       10/396       24/396       0.31 (0.26-0.3)         istation       32/138       15/60       0.29 (0.25-0.2)	0.08 (7) (0.35 (5) (5) (7) (7) (7) (7) (7) (7) (7) (7
ABCEGH 31/49 12/47 AGH 290/580 126/583 Overall	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.31 (0.26-0.3)       0.26 (0.20-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.26 (0.20-0.3)         core       0.7/223       40/221       0.29 (0.25-0.3)         n       11/13       9/24       0.26 (0.28-0.3)         domization       361/596       165/603       0.29 (0.25-0.3)         ormance status       361/596       165/603       0.30 (0.25-0.3)         ormance status       33/213       58/215       0.30 (0.25-0.3)         opp planned       133/213       58/215       0.30 (0.25-0.4)         disease       110/396       24/396       0.31 (0.26-0.3)         110/396       24/396       0.31 (0.26-0.3)       0.33 (0.25-0.4)         disease       514/919       233/900       0.27 (0.23-0.3)       0.31 (0.26-0.4)         disease       514/919       233/900       0.29 (0.25-0.3)       0.31 (0.26-0.4)         disease       514/919       23/900       0.29 (0.25-0.4)       0.32 (0.16-0.6)	0.08 7 0.35 5 5 0.35 0.35 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.25 0.25 0.29 0.02 0.04 0.29 0.04 0.29 0.04 0.35 0.29 0.02 0.04
AGH 290/580 126/583	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.31 (0.26-0.3)       0.26 (0.20-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.26 (0.20-0.3)         core       0.7/223       40/221       0.24 (0.18-0.3)         n       11/13       9/24       0.26 (0.22-0.3)         domization       361/596       165/603       0.29 (0.25-0.3)         ormance status       361/596       165/603       0.26 (0.22-0.3)         ormance status       31/4/361       83/357       0.36 (0.28-0.4)         opp planned       394/718       179/714       -       0.30 (0.25-0.43)         topp planned       110/396       24/396       0.31 (0.26-0.30)       0.33 (0.25-0.43)         disease       514/919       233/900       -       0.31 (0.26-0.30)       0.33 (0.25-0.43)         disease       514/919       233/900       -       0.31 (0.26-0.30)       0.33 (0.25-0.34)         disease       514/919       233/900       -       0.31 (0.26-0.30)       0.32 (0.16-0.61)         di       21/38       15/60       0.22 (0.16-0.61)       0.32	0.08 7 0.35 5 5 0.35 0.35 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.73 0.25 0.25 0.29 0.02 0.04 0.29 0.04 0.29 0.04 0.35 0.29 0.02 0.04
Overall	status     0.21 (0.15-0.3)       astatic     142/455     38/460       us     0.21 (0.15-0.3)       us     0.26 (0.20-0.32)       us     0.29 (0.24-0.33)       orde     0.29 (0.25-0.32)       orde     0.26 (0.22-0.32)       orde     0.31 (0.26-0.32)       orde     0.30 (0.25-0.32)       orde     0.30 (0.25-0.32)       orde     0.30 (0.25-0.32)       orde     0.31 (0.26-0.32)       orde     0.32 (0.18-0.32)       orde     0.31 (0.26-0.32)       orde     0.31 (0.26-0.32)       orde<	0.08 (7) (0.35 (5) (5) (7) (7) (7) (7) (7) (7) (7) (7
	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.44 (0.24-0.8)         core       0.7/223       40/221       0.44 (0.24-0.8)         n       11/13       9/24       0.50 (0.20-0.3)         domization       361/596       165/603       0.29 (0.25-0.3)         ormance status       0.15 (0.05-0.4)       0.26 (0.20-0.3)         in 11/13       9/24       0.50 (0.28-0.3)         aspirin use       361/596       165/603       0.26 (0.22-0.3)         i33/213       58/215       0.30 (0.25-0.4)       0.30 (0.25-0.4)         i33/213       58/215       0.30 (0.25-0.4)       0.30 (0.25-0.4)         i33/213       58/215       0.31 (0.26-0.4)       0.33 (0.25-0.4)         ipp planned       133/213       58/215       0.31 (0.26-0.3)         idisease       110/396       24/396       0.31 (0.26-0.3)         idisease       514/919       233/900       0.32 (0.16-0.3)         idisease       514/919       233/900       0.33 (0.26-0.4)	0.08 7 0.35 5 5 5 0.35 5 0.73 8 0.25 10 0.5 10 0.5 10 0.5 10 0 0 0 0 0 0 0 0 0 0
	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.44 (0.24-0.8)         core       0.7/223       40/221       0.44 (0.24-0.8)         n       11/13       9/24       0.50 (0.20-0.3)         domization       361/596       165/603       0.29 (0.25-0.3)         ormance status       0.15 (0.05-0.4)       0.26 (0.20-0.3)         in 11/13       9/24       0.50 (0.28-0.3)         aspirin use       361/596       165/603       0.26 (0.22-0.3)         i33/213       58/215       0.30 (0.25-0.4)       0.30 (0.25-0.4)         i33/213       58/215       0.30 (0.25-0.4)       0.30 (0.25-0.4)         i33/213       58/215       0.31 (0.26-0.4)       0.33 (0.25-0.4)         ipp planned       133/213       58/215       0.31 (0.26-0.3)         idisease       110/396       24/396       0.31 (0.26-0.3)         idisease       514/919       233/900       0.32 (0.16-0.3)         idisease       514/919       233/900       0.33 (0.26-0.4)	0.08 7 0.35 5 5 5 0.35 5 0.73 8 0.25 10 0.5 10 0.5 10 0.5 10 0 0 0 0 0 0 0 0 0 0
	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.44 (0.24-0.8)         core       107/223       40/221       0.29 (0.25-0.3)         n       11/13       9/24       0.29 (0.25-0.3)         domization       361/596       165/603       0.26 (0.20-0.3)         orrance status       0.36 (0.28-0.4)       0.30 (0.25-0.3)         orrance status       11/1/3       9/24       0.26 (0.22-0.3)         aspirin use       394/718       179/714       0.30 (0.25-0.3)         333 (0.25-0.4)       0.33 (0.25-0.4)       0.33 (0.25-0.4)         (11/239)       69/246       0.33 (0.25-0.4)         (13/213)       58/215       0.33 (0.25-0.4)         (10/396)       24/396       0.33 (0.25-0.4)         (10/396)       24/396       0.31 (0.26-0.3)         (10/38)       15/60       0.33 (0.25-0.4)         (11/38)       15/60       0.33 (0.25-0.4)         (11/38)       15/60       0.33 (0.25-0.4)         (11/38)	0.08 (7) (0.35 (5) (5) (7) (7) (8) (7) (7) (7) (7) (7) (7) (7) (7
0.2 0.3 0.4 0.5 0.6 0.7 0.3	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       393/502       210/500       0.21 (0.15-0.3)         us       323/483       160/484       0.26 (0.20-0.35)         ninate       28/36       19/42       0.44 (0.24-0.86)         core       107/223       40/221       0.42 (0.18-0.33)         n       11/13       9/24       0.15 (0.05-0.48)         domization       361/596       165/603       0.26 (0.22-0.33)         ormance status       174/361       83/357       0.26 (0.22-0.33)         aspirin use       394/718       179/714       0.25 (0.18-0.34)         aspirin use       394/718       179/714       0.27 (0.23-0.32)         upp planned       425/561       224/564       0.31 (0.26-0.34)         disease       514/919       233/900       0.33 (0.25-0.43)         did       21/38       15/60       0.33 (0.26-0.43)         did       21/38       15/60       0.33 (0.26-0.34)         disease       0.31 (0.26-0.34)       0.33 (0.25-0.34)       0.33 (0.25-0.43)         disease       0.13 (0.26-0.34)       0.33 (0.25-0.34)       0.33 (0.25-0.43)         disease	0.08 (7) (0.35 (5) (5) (7) (7) (8) (7) (7) (7) (7) (7) (7) (7) (7
•	status       0.21 (0.15-0.3)         astatic       142/455       38/460       0.21 (0.15-0.3)         us       0.21 (0.15-0.3)       0.31 (0.26-0.3)         us       323/483       160/484       0.29 (0.24-0.3)         ninate       28/36       19/42       0.44 (0.24-0.8)         core       107/223       40/221       0.29 (0.25-0.3)         n       11/13       9/24       0.29 (0.25-0.3)         domization       361/596       165/603       0.26 (0.20-0.3)         orrance status       0.36 (0.28-0.4)       0.30 (0.25-0.3)         orrance status       11/1/3       9/24       0.26 (0.22-0.3)         aspirin use       394/718       179/714       0.30 (0.25-0.3)         333 (0.25-0.4)       0.33 (0.25-0.4)       0.33 (0.25-0.4)         (11/239)       69/246       0.33 (0.25-0.4)         (13/213)       58/215       0.33 (0.25-0.4)         (10/396)       24/396       0.33 (0.25-0.4)         (10/396)       24/396       0.31 (0.26-0.3)         (10/38)       15/60       0.33 (0.25-0.4)         (11/38)       15/60       0.33 (0.25-0.4)         (11/38)       15/60       0.33 (0.25-0.4)         (11/38)	0.08 7) 0.35 5) 5) 0.73 8) 0.73 8) 0.73 8) 0.73 8) 0.73 9) 0.25 10 0.29 10 0.29 10 0.29 10 0.49 4) 0.34 10 0.34 10 0.34 10 0.34

# Figure 2. 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 antiinflammatory drug.

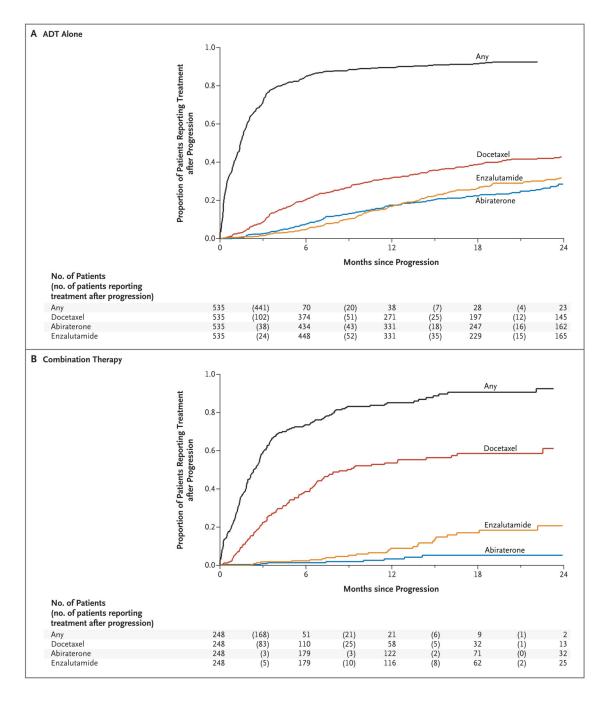


Figure 3. Time until the Initiation of Second-Line Treatment after First Event of Radiologic, Clinical, or PSA Progression.

#### Table 1

## Characteristics of the Patients.\*

Characteristic	<b>ADT Alone</b> (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. $(\%)^{\dagger}$		
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. $(\%)^{\ddagger}$		
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.

<sup>†</sup>The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.

 $\ddagger$ Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis.

<sup>§</sup>All patients with planned use of luteinizing hormone-releasing hormone (LHRH) analogues should have antiandrogens for disease flares, at least.

 ${}^{\it M}$ Data were missing for one patient in the ADT-alone group.

<sup>//</sup>Radiotherapy was mandated for patients with newly diagnosed node-negative, nonmetastatic disease and strongly encouraged in patients with newly diagnosed node-positive, nonmetastatic disease.

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 $^{\dagger}$	3 (<1)	9 (1)
Grade 3-5 adverse events - no. (	%)	
Endocrine disorders <sup>‡</sup>	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 $^{\dagger}$	3 (<1)	9 (1)

\* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

 $^{\dagger}$ 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.

<sup>*i*</sup>Endocrine disorders included hot flashes and impotence.