Casodex® Study

Journal/Year	*The Journal of Urology*, 2000
Author(s)	Iversen P, Tyrrell CJ, Kaisary AV, et al
Title	Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of follow-up
Study Design	Pooled data from 2 open-label, multicenter studies of identical design
Patient Population Studied	480 patients with locally advanced (M0) or metastatic (M1) prostate cancer
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • PSA ≥20 ng/mL • T3/T4 locally advanced (M0) or metastatic (M1) prostate cancer Exclusion: • Previous systemic therapy for prostate cancer • Radiotherapy during previous 3 months • Invasive malignancy previous 5 years • ECOG performance score of 3 or 4
Treatment Arm	100 or 150 mg tablet bicalutamide daily
Comparator Arm	Orchiectomy (surgical castration) OR goserelin acetate 3.6 mg administered by subcutaneous injection every 28 days (medical castration)
Primary Endpoint(s)	• Time to death • Objective progression
Secondary Endpoint(s)	Quality of life was also assessed at 4, 12, 24 and 48 weeks after randomization using a self-administered, validated questionnaire.
Efficacy Outcomes	• Of 480 patients with M0 disease at study entry, 320 patients were randomized to receive bicalutamide monotherapy, 138 patients to medical castration, and 22 patients to surgical castration • At median follow-up of 6.3 years, mortality was 56%; disease had progressed in 368 of the 480 patients (77%) • There was no statistical difference in OS between the 2 groups (HR = 1.05, 2-sided 95% CI 0.81, 1.36, upper 1-sided 95% CL 1.31, *P* = 0.70) • Median survival was 63.5 months in the bicalutamide group vs 69.9 months in the castration group • There was no statistically significant difference in time to progression between patients in the bicalutamide and patients in the castration groups (HR = 1.20; 2-sided 95% CI 0.96, 1.51; upper 1-sided 95% CL 1.452, *P* = 0.11) • There were statistically significant benefits for patients treated with bicalutamide relative to those treated with castration in the quality of life domains of sexual interest (*P* = 0.029) and physical capacity (assesses activities such as walking, dressing, bathing, shopping, climbing stairs, sports and bending) (*P* = 0.046) after 12 months of treatment. Differences in favor of bicalutamide were found in 6 other domains, although they were not statistically significant. In only 1 domain was a nonsignificant difference in favor of castration recorded.
Selected Safety Data	The overall incidence of AEs was similar in the 2 treatment groups, and occurred in at least 10% of patients in each group Highest AEs were pharmacological side effects of: • Hot flashes in the castration group (50.0% castration versus 13.1% of bicalutamide groups) • Breast pain (40.1%) and gynecomastia (49.4%) in the bicalutamide group
Selected Treatment Discontinuation Data %	• Withdrawals due to drug-related AEs in the bicalutamide group were low (4.1%)
Summary of Authors' Conclusions	• There was no statistically significant difference in OS or time to progression between patients in the bicalutamide 150 mg monotherapy group and patients in the castration group after follow-up of 6.3 years • Monotherapy with bicalutamide 150 mg was characterized as an attractive alternative to castration in patients where immediate hormone therapy is indicated

Sourced from:

1. Iversen P, Tyrrell CJ, Kaisary AV, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *J Urol*. 2000;164:1579-1582.
2. Iversen P, Tyrrell CJ, Kaisary AV, et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology*. 1998;51:389-396.

CHAARTED Study

Journal/Year	*The New England Journal of Medicine*, 2015
Author(s)	Sweeney C, Chen Y, Carducci M, et al
Title	Chemohormonal therapy in metastatic hormone-sensitive prostate cancer
Study Design	Phase 3, randomized trial
Patient Population Studied	790 men with metastatic, hormone-sensitive prostate cancer
Selected Patient Inclusion Criteria	Inclusion: • Pathological diagnosis of prostate cancer or clinical scenario consistent with prostate cancer with elevated PSA • Radiologic evidence of metastatic disease • ECOG performance status score of 0, 1, or 2 • Prior adjuvant androgen deprivation therapy (ADT) if the duration of therapy was ≤24 months progression and had occurred >12 months after therapy completion • ADT for metastatic disease with no evidence of progression and treatment commenced within 120 days before randomization • Organ function adequate for docetaxel treatment
Treatment Arm	• ADT plus docetaxel (IV) 75 mg per square meter of body surface area given every 3 weeks for 6 cycles. • Premedication included oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before docetaxel infusion. • Daily prednisone was not required.
Comparator Arm	ADT alone
Primary Endpoint(s)	OS
Secondary Endpoint(s)	• Decrease in the PSA level to less than 0.2 ng per milliliter at 12 months and 6 months • Time to castration-resistant prostate cancer • Time to clinical progression
Efficacy Outcomes	• The median overall survival was 13.6 months longer with docetaxel in combination with ADT vs ADT alone (median OS 57.6 months vs 44.0 months; hazard ratio for death in the combination group, 0.61; 95% confidence interval [CI], 0.47 to 0.80; $P < 0.001$) • In the subgroup with high-volume disease, median overall survival was 17.0 months longer in the docetaxel plus ADT group compared to the ADT-alone group (49.2 months vs 32.2 months; hazard ratio for death, 0.60; 95% CI, 0.45 to 0.81; $P < 0.001$) • The proportion of patients who had a decrease in the PSA level to less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group, as compared with 16.8% in the ADT-alone group ($P < 0.001$)
Selected Safety Data	Combination therapy, grade 3 or 4 AEs: • Allergic reaction (approximately 2%) • Fatigue (4%) • Diarrhea, stomatitis, motor neuropathy, and sensory neuropathy (≤1%) • Thromboembolic event (approximately 1%) • Neutropenic fever (6%) • Infection with neutropenia (approximately 2%) The AE profile of ADT was assumed to be common to the two groups. The potential risk of ascertainment bias for adverse events and early progression in the ADT-plus-docetaxel group was recognized, but such bias, if it existed, would have favored the ADT-alone group.

Summary of Authors' Conclusions	Docetaxel given at the time ADT was initiated for metastatic hormone-sensitive disease resulted in: • Better cancer control than with ADT alone with a longer time to development of castration resistance. The median time to the development of castration-resistant prostate cancer (biochemical, symptomatic, or radiographic) was 20.2 months with combination therapy, as compared with 11.7 months with ADT alone (hazard ratio in the combination group, 0.61; 95% CI, 0.51 to 0.72; *P* < 0.001). • A higher rate of decrease of PSA level to <0.2 ng/mL at 12 months. The proportion of patients who had a decrease in the PSA level to less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group, as compared with 16.8% in the ADT-alone group (*P* < 0.001). • A lower number of prostate-cancer deaths with 85 prostate-cancer deaths in the combination group and 114 prostate-cancer deaths in the ADT-alone group • Substantially longer OS. The benefit at the last analysis was more apparent in the subgroup with high-volume disease than in the overall study population, with a median overall survival that was 17.0 months longer in the combination group than in the ADT-alone group (49.2 months vs. 32.2 months; hazard ratio for death, 0.60; 95% CI, 0.45 to 0.81; *P* < 0.001).

Sourced from:

1. Sweeney C, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015;373:737-746.
2. ClinicalTrials.gov. Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED). https://clinicaltrials.gov/ct2/show/NCT00309985. Accessed November 20, 2017.

LATITUDE Study

Journal/Year	*The New England Journal of Medicine*, 2017
Author(s)	Fizazi K, Tran N, Fein L, et al
Title	Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer
Study Design	Phase 3, randomized, double-blind, placebo-controlled trial
Patient Population Studied	• 1199 patients with high-risk, metastatic castration-sensitive prostate cancer (mCSPC) • Documented by a positive bone scan or metastatic lesions at time of diagnosis on computed tomography (CT) or magnetic resonance imaging (MRI), according to RECIST version 1.1
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • At least 18 years of age • ECOG performance status score of 0 to 2 • Newly diagnosed pathologically confirmed prostate cancer without neuroendocrine differentiation or small-cell histologic features • At least two of the three high-risk factors associated with poor prognosis: Gleason score of ≥8, ≥3 bone lesions, and the presence of measurable visceral metastasis Exclusion: • Previous chemotherapy, radiation therapy, or surgery for metastatic prostate cancer with the exception of: – ≤3 months ADT with luteinizing hormone-releasing hormone analogues – Orchiectomy with/without concurrent first -generation androgen-receptor antagonists before baseline – One course palliative radiation or surgical therapy treating symptoms associated with metastatic disease
Treatment Arm	ADT + abiraterone acetate (1000 mg PO QD, four 250-mg tablets) plus prednisone (5 mg PO QD)
Comparator Arm	ADT + dual placebos
Co-Primary Endpoint(s)	• OS • rPFS
Secondary Endpoint(s)	• Time to the next "skeletal-related event" • Time to progression with respect to prostate-specific antigen (PSA) level on the basis of Prostate Cancer Working Group 2 criteria • Time to the next therapy for prostate cancer • Time to initiation of chemotherapy • Time to pain progression
Efficacy Outcomes	• The OS at 3 years was 66% in the abiraterone acetate plus prednisone in combination with ADT arm and 49% in the ADT plus dual placebos arm • At 3 years, median OS was significantly longer in the abiraterone acetate plus prednisone in combination with ADT arm than ADT plus placebos arm (not reached vs 34.7 months) (HR for death = 0.62; 95% CI: 0.51 to 0.76; ($P < 0.001$) • Median rPFS was 33.0 months for the abiraterone acetate plus prednisone in combination with ADT arm and 14.8 months for the ADT plus placebos arm (HR for disease progression or death = 0.47; 95% CI: 0.39 to 0.55; $P < 0.001$) • The superiority of abiraterone acetate over placebo was shown for all secondary endpoints. The numbers of patients who received one or multiple life-prolonging subsequent therapies were 125 (21%) in the abiraterone acetate plus prednisone in combination with ADT arm and 246 (41%) in the ADT plus placebos arm. Docetaxel was the most common post-progression treatment in the two groups.

Selected Safety Data	Grade 3 or 4 adverse events were reported in 63% of the patients abiraterone acetate plus prednisone in combination with ADT arm and in 48% of those in the ADT plus placebos arm The numbers of patients with serious AEs were similar in the two groups Grade 3 mineralocorticoid-related toxic effects occurred at a higher frequency in abiraterone acetate plus prednisone in combination with ADT arm vs ADT plus placebos arm: • Grade 3 and grade 4 hypertension rates were 20% and 0% vs 10% and 0.2% • Grade 3 and grade 4 hypokalemia 10% and 0.8% vs 1% and 0.2%
Selected Treatment Discontinuation Data, %	• 12% in the abiraterone acetate plus prednisone in combination with ADT arm • 10% in the ADT plus placebos arm
Summary of Authors' Conclusions	Addition of abiraterone acetate and prednisone to ADT in men with newly diagnosed mCSPC: • Significantly increased OS (38% lower relative risk of death [HR = 0.62] in the abiraterone acetate plus prednisone in combination with ADT arm. Median overall survival was significantly longer in the abiraterone acetate plus prednisone in combination with ADT arm than in the ADT plus placebos arm (not reached vs 34.7 months) (hazard ratio for death, 0.62; 95% confidence interval [CI], 0.51 to 0.76; *P* < 0.001). • Significantly increased rPFS (HR = 0.47). The median length of radiographic progression-free survival was 33.0 months in the abiraterone acetate plus prednisone in combination with ADT arm and 14.8 months in the ADT plus placebos arm (hazard ratio for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; *P* < 0.001).

Sourced from:

1. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. *N Engl J Med*. 2017;377:352-60.

LURON Study

Journal/Year	*The Journal of Urology*,1990
Author(s)	Sharifi R, Soloway M, The Leuprolide Study Group
Title	Clinical study of leuprolide depot formulation in the treatment of advanced prostate cancer
Study Design	• Phase 3, open, multicenter study
Patient Population Studied	• 56 patients with stage D2 prostate cancer • No previous systemic treatment
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Histologically confirmed stage D2 prostate carcinoma • ≥2 clinically measurable or evaluable manifestations of prostate cancer • Pre-study serum testosterone levels of ≥150 ng/dL • ECOG performance status score of ≤2 • No systemic treatment other than local radiation therapy • Local radiation therapy permitted provided irradiated site not used as an evaluable lesion and ≥2 evaluable lesions remained Exclusion: • Previous chemotherapy or hormonal manipulation • Life-threatening renal, hepatic, or cardiovascular disease • Life expectancy of <3 months
Treatment Arm	Leuprolide depot formulation (7.5 mg injected intramuscularly every 4 weeks)
Comparator Arm	None
Primary Endpoint(s)*	• Serum testosterone, luteinizing hormone, and plasma leuprolide levels were monitored during the 24-week study period • Objective response rate • Median survival time • Performance status • Safety
Secondary Endpoint(s)	—
Efficacy Outcomes	Objective response (no progression) to treatment occurred in 81% of 53 evaluable patients • Mean testosterone levels decreased to within the castrate range by week 3 of treatment • Median interval to onset of castrate testosterone levels was 21 days • Of 31 patients with an abnormal performance status (>0) at baseline, 42% had improved performance at week 12 and 52% remained stable, for a total of 94% improvement or stable • At week 24, 8 patients (18.2%) had progression • No worsening in performance status
Selected Safety Data	Hot flashes occurred in 32 patients (57%). Six patients (10.7%) who had hot flashes also reported sweating. Reactions (other than hot flashes) in ≥5% of the patients included: • Peripheral edema • Constipation • Chest pain • Urinary frequency • Pain • Dyspnea • Impotence
Selected Treatment Discontinuation Data	10 patients were discontinued from the study before 24 weeks: 3 died (2 of prostate cancer at weeks 11 and 24, and 1 of septicemia at week 24); 4 had disease progression at weeks 8, 15, 24 and 24; 2 were discontinued for early protocol violation at weeks 2 and 7; and 1 had an adverse event (testicular pain) at week 24.
Summary of Authors' Conclusions	Depot formulation of leuprolide is safe and effective in the treatment of advanced prostatic cancer, and that the safety and efficacy of the formulation do not differ significantly from those of the daily subcutaneous formulation.

* Endpoints were not identified as primary or secondary in this publication.

Sourced from:

1. Sharifi R, Soloway M, The Leuprolide Study Group. Clinical study of leuprolide depot formulation in the treatment of advanced prostate cancer. *J Urol*. 1990;143:68-71.

PREVAIL Study

Journal/Year	*The New England Journal of Medicine*, 2014
Author(s)	Beer TM, Armstrong AJ, Rathkopf DE, et al
Title	Enzalutamide in metastatic prostate cancer before chemotherapy
Study Design	• Phase 3, randomized, double-blind, placebo-controlled, multinational study
Patient Population Studied	• 1717 patients with metastatic castration-resistant prostate cancer • No previous chemotherapy
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Histologically/cytologically confirmed adenocarcinoma of the prostate with documented metastases • PSA progression, radiographic progression, or both in bone or soft tissue, despite luteinizing hormone–releasing hormone (LHRH) analogue therapy or undergoing orchiectomy • Serum testosterone level of ≤1.73 nmol per liter (50 ng per deciliter) • Continued ADT • Patients had not received cytotoxic chemotherapy, ketoconazole, or abiraterone acetate • ECOG performance status score of 0 or 1 • Brief Pain Inventory Short Form (BPI-SF) question 3 asymptomatic (score of 0 or 1) or mildly symptomatic (2 to 3) Exclusion • History of seizure/condition that could confer predisposition to seizure
Treatment Arm	Oral enzalutamide (at a dose of 160 mg) QD with or without food
Comparator Arm	Placebo once QD with or without food
Co-Primary Endpoint(s)	• OS • Radiographic progression-free survival (rPFS)
Secondary Endpoint(s)	• Time until initiation of cytotoxic chemotherapy • Time until first skeletal-related event • Best overall soft-tissue response • Time until PSA progression • Decline in PSA of 50% or more from baseline
Efficacy Outcomes	• At 12 months of follow-up, the rate of rPFS was 65% in the enzalutamide group and 14% in the placebo group • Treatment with enzalutamide, compared with placebo, resulted in an 81% reduction in the risk of radiographic progression or death (enzalutamide group; the median rPFS was not reached in the enzalutamide group, as compared with 3.9 months in the placebo group (HR = 0.19; 95% CI: 0.15 to 0.23; $P < 0.001$) • Fewer patients in the enzalutamide group than the placebo group had radiographic progression or died (118 of 832 patients [14%] vs 321 of 801 patients [40%]) • At the planned interim analysis of OS, the median duration of follow-up for survival was approximately 22 months. Fewer deaths occurred in the enzalutamide group than in the placebo group (241 of 872 patients [28%] vs 299 of 845 patients [35%]). Treatment with enzalutamide, as compared with placebo, resulted in a 29% decrease in the risk of death. Median OS was estimated at 32.4 months in the enzalutamide group and 30.2 months in the placebo group (hazard ratio, 0.71; 95% CI, 0.60 to 0.84; $P < 0.001$) • Benefit of enzalutamide was shown with respect to all secondary endpoints, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs 3%) ($P < 0.001$ for all comparisons)

Selected Safety Data	• The most common AEs in ≥10% of the patients in the enzalutamide group were: – Fatigue – Back pain – Constipation – Arthralgia – Decreased appetite – Hot flush – Diarrhea – Hypertension – Asthenia – Fall – Weight loss – Headache • The most common grade 3 or higher event in the enzalutamide group was hypertension (7%) • Seizure, which was previously observed in the enzalutamide group among patients who had received chemotherapy, occurred in a single patient (0.1%) in each group in the study. Both patients had a history of seizure that was unknown to investigators at the time of enrollment
Selected Treatment Discontinuation Data, %	• A similar proportion of patients in each group (6%) discontinued treatment because of an adverse event
Summary of Authors' Conclusions	Enzalutamide: • Extended the time until radiographic progression or death • Improved OS • Delayed the initiation of chemotherapy by median of 17 months

Sourced from:

1. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014;371:424-433.

STAMPEDE Study

Journal/Year	*The New England Journal of Medicine*, 2017
Author(s)	James ND, deBono JS, Spears MR, et al
Title	Abiraterone for prostate cancer not previously treated with hormone therapy
Study Design*	Multi-group, multi-stage (also called multi-arm, multi-stage [MAMS] platform design), and multi-center randomized controlled trial
Patient Population Studied	1917 patients with: • Newly diagnosed, locally advanced disease, or • Newly diagnosed, metastatic disease, or • Relapsing disease with poor prognostic features
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Prostate cancer that was: – Newly diagnosed and metastatic, node-positive, or high-risk, locally advanced (defined as having ≥2 of the following disease characteristics: a tumor stage of T3 or T4, Gleason score of 8 to 10, and PSA level ≥40 ng/mL), OR – Disease previously treated with radical surgery or radiotherapy now relapsing with high-risk features (defined as a PSA level >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse, or <12 months of total ADT with an interval of >12 months without treatment) – Had not previously received hormone therapy and were intended for long-term ADT started ≤12 weeks before randomization Exclusion: • Clinically significant cardiovascular disease
Treatment Arm	ADT + abiraterone acetate (1000 mg) and prednisolone (5 mg) (combination therapy) QD
Comparator Arm	ADT (control)
Primary Endpoint(s)	• OS • The intermediate primary outcome was failure-free survival, defined as the time to the first of the following forms of treatment failure: biochemical (PSA) failure; progression of local, lymph-node, or distant metastases; or death from prostate cancer
Secondary Endpoint(s)	• Adverse events • Symptomatic skeletal events • Progression-free survival (ie, failure-free survival excluding biochemical failure) • Prostate cancer–specific survival • Quality of life (data not shown)

Efficacy Outcomes	• 184 deaths occurred in the combination group vs 262 in ADT-alone group. The 3-year survival rate was 83% in the ADT + abiraterone acetate and prednisolone group compared with 76% in the ADT-alone group (HR = 0.63; 95% CI: 0.52 to 0.76; *P* < 0.001); HR = 0.75 (nonmetastatic disease) and 0.61 (metastatic disease). • 248 treatment-failure events occurred in the combination group vs 535 in ADT-alone group. The 3-year failure-free survival was 75% in the ADT + abiraterone acetate and prednisolone group compared to 45% in the ADT-alone group (HR = 0.29; 95% CI: 0.25 to 0.34; *P* < 0.001); HR = 0.21 (nonmetastatic disease) and 0.31 (metastatic disease). • The 3-year progression-free survival was 80% in the ADT + abiraterone acetate and prednisolone group and 62% in the ADT-alone group (hazard ratio for clinical or radiologic progression or death from prostate cancer, HR = 0.40; 95% CI, 0.34 to 0.47; *P* < 0.001). • The 3-year rate without symptomatic skeletal events was 88% in the ADT + abiraterone acetate and prednisolone group and 78% in the ADT-alone group (hazard ratio for symptomatic skeletal events, (HR = 0.46; 95% CI, 0.37 to 0.58; *P* < 0.001). • 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).
Selected Safety Data	• The amount of patients in the safety population who reported adverse events of grade 3 or higher during their entire time in the trial was 47% in the combination group and 33% in the ADT-alone group. • 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). Main additional AEs over and above the control therapy were: • Hypertension • Mild increases in aminotransferase levels • Respiratory disorders
Selected Treatment Discontinuation Data, %	Combination group: • 51% for progression • 20% excessive toxic effects
Summary of Authors' Conclusions	ADT + abiraterone acetate and prednisolone had significantly higher rates of overall and failure-free survival than ADT alone.

*This slide is a summary of the results of the specific arm that evaluated abiraterone acetate plus prednisolone in combination with ADT compared to ADT alone.

Sourced from:

1. James ND, deBono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med.* 2017;377:338-351.

STRIVE Study

Journal/Year	*Journal of Clinical Oncology*, 2016
Author(s)	Penson DF, Armstrong AJ, Concepcion R, et al
Title	Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial
Study Design	Phase 2, multicenter, randomized, double-blind trial
Patient Population Studied	396 men with nonmetastatic or mCRPC
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Histologically or cytologically confirmed adenocarcinoma of the prostate • Serum testosterone level ≤50 ng/dL (1.73 nmol/L) • Progressive disease despite ADT Exclusion: • Prior disease progression while receiving bicalutamide • Prior chemotherapy • Prior radiation for distant metastasis • Systemic corticosteroids for prostate cancer • History of seizure
Treatment Arm	• Enzalutamide 160 mg per day (oral; four 40 mg capsules + placebo capsule) • ADT maintained throughout
Comparator Arm	• Bicalutamide 50 mg per day (oral; one capsule + four placebo capsules) • ADT maintained throughout
Primary Endpoint(s)	PFS
Secondary Endpoint(s)	• Time to PSA progression • Proportion of patients with a ≥50% PSA response • rPFS in metastatic patients
Efficacy Outcomes	• Enzalutamide reduced the risk of progression or death by 76% vs. bicalutamide (HR = 0.24; 95% CI: 0.18 to 0.32; $P < 0.001$) • Median PFS was 19.4 months in the enzalutamide treatment group vs 5.7 months in the bicalutamide treatment group • The treatment effect of enzalutamide on PFS was consistently favorable across all prespecified subgroups, including disease state (nonmetastatic vs metastatic) at study entry. In patients with nmCRPC, median PFS was not reached with enzalutamide compared with 8.6 months with bicalutamide (HR = 0.24; 95% CI: 0.14 to 0.42). In patients with mCRPC, median PFS was 16.5 months with enzalutamide and 5.5 months with bicalutamide (HR = 0.24; 95% CI: 0.17 to 0.34). • Enzalutamide resulted in significant improvements in all key secondary endpoints. Enzalutamide was associated with a decrease in the risk of radiographic progression or death compared with bicalutamide in both metastatic and nonmetastatic disease: 68% (HR = 0.32; 95% CI: 0.21 to 0.50; $P < 0.001$) and 76% (HR = 0.24; 95% CI: 0.10 to 0.56), respectively. The median rPFS in those with metastatic disease was not reached with enzalutamide compared with 8.3 months with bicalutamide. (HR = 0.32; 95% CI: 0.21 to 0.50; $P < 0.001$).

Selected Safety Data	Serious adverse events, grade ≥3 adverse events, and adverse events resulting in death were reported at similar rates in both treatment groups. Common AEs that occurred in ≥10% of patients in the enzalutamide treatment arm: • Fatigue • Back pain • Hot flashes • Fall • Hypertension • Dizziness • Decreased appetite Common AEs that occurred in ≥10% of patients in the bicalutamide treatment arm: • Diarrhea • Anemia • Urinary tract infection • Constipation
Selected Treatment Discontinuation Data, %	Enzalutamide: • Disease progression 29.3% • AEs 8.1% Bicalutamide: • Disease progression 70.2% • AEs 6.1%
Summary of Authors' Conclusions	Enzalutamide significantly reduced risk of prostate cancer progression or death by 76% compared with bicalutamide in patients with nonmetastatic or mCRPC.

Sourced from:

1. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE trial. *J Clin Oncol*. 2016;34:2098- 2113.

TERRAIN Study

Journal/Year	*The Lancet Oncology*, 2016
Author(s)	Shore ND, Chowdhury S, Villers A, et al
Title	Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study
Study Design	Phase 2, multinational, randomized, double-blind trial
Selected Patient Population Studied	375 asymptomatic or minimally symptomatic men with mCRPC with progression on ADT
Patient Inclusion/Exclusion Criteria	Inclusion: • Histologically confirmed adenocarcinoma of the prostate with documented metastases • Testosterone concentration ≤1.7 nmol/L (50 ng/dL) • Disease progression on ADT • Asymptomatic or mildly symptomatic prostate cancer • Not using opiate analgesics for prostate cancer-related pain • ECOG performance status score of 0 or 1 • Life expectancy of at least 12 months Exclusion: • Previous progression on antiandrogen therapy • Previous chemotherapy • Brain metastasis • History of seizure • Severe concurrent disease • Active epidural disease • Other malignancy • Clinically significant cardiovascular disease • Gastrointestinal disease affecting absorption
Treatment Arm	• Enzalutamide 160 mg/day, orally (4 capsules) + placebo tablet • ADT with an LHRH agonist or antagonist, or bilateral orchiectomy
Comparator Arm	• Bicalutamide 50 mg/day, orally (one tablet) + 4 placebo capsules • ADT with an LHRH agonist or antagonist, or bilateral orchiectomy
Primary Endpoint(s)	PFS
Secondary Endpoint(s)	• Safety • Investigator-review-based PFS • Time to PSA progression • PSA response by week 13 • Best PSA response

Efficacy Outcomes	• Patients in the enzalutamide group had a significantly improved median PFS of 15.7 months (95% CI: 11.5 to 19.4) vs 5.8 months in the bicalutamide group (95% CI: 4.8 to 8.1); (HR = 0.44; 95% CI: 0.34 to 0.57; *P* < 0.0001) • The beneficial treatment effect of enzalutamide on PFS compared with bicalutamide was consistent across all prespecified subgroups. • Median investigator-based progression-free survival was 15.3 months (95% CI: 11.8 to19.4) for patients in the enzalutamide group and 5.7 months (5.4 to 8.1) in the bicalutamide group (HR = 0.42; 95% CI: 0.33 to 0.55; *P* < 0.0001). • Median time to a PSA progression event was 19.4 months (95% CI: 16.6 to not reached) for patients assigned to enzalutamide and 5.8 months (5.6–8.3) for patients assigned to bicalutamide (HR = 0.28; 95% CI: 0.20 to 0.39; *P* < 0.0001). • The median change in PSA concentration from baseline by week 13 was greater in the enzalutamide group than in the bicalutamide group (*P* < 0.0001). Additionally, the median best PSA response at any point after the start of treatment was a decrease of 93% (IQR –98.4 to –74.7) and an increase of 0.18% (–49.2 to 79.0) for the enzalutamide and bicalutamide groups, respectively (*P* < 0.0001).
Selected Safety Data	AEs occurring more frequently with: • Enzalutamide: fatigue, back pain, hot flush, hypertension, diarrhea, weight decrease, and pain in the extremities: • Bicalutamide: nausea, constipation, and arthralgia Most common ≥ grade 3 AEs occurring in ≥ 2% of patients in either treatment group: • Hypertension • Hydronephrosis • Back pain • Pathological fracture • Bone pain • Congestive cardiac failure • Myocardial infarction • Anemia • Dyspnea ≥ Grade 3 cardiac AEs were reported in 5% of patients in the enzalutamide group and 2% of patients in the bicalutamide group during the course of the study, with an increased incidence of ≥ grade 3 cardiac AEs in the enzalutamide group noted later in the study (after ≥ 6 months on the study drug) when there was a greater imbalance in exposure by treatment group. Of the 9 deaths in the enzalutamide group, one was reported as being possibly related to the study drug (systemic inflammatory response syndrome) compared with none of the 3 deaths in the bicalutamide group. Two patients in the enzalutamide group had seizures; one was diagnosed with a brain tumor after presenting with seizure, and the other had an undisclosed childhood and family history of seizures and had his event after a traumatic head injury. One patient in the bicalutamide group had a hypoglycemic seizure.
Selected Treatment Discontinuation Data %	126 (68%) patients in the enzalutamide arm and 168 (88%) patients in the bicalutamide arm, respectively, discontinued their assigned treatment before study end, mainly due to progressive disease.
Summary of Authors' Conclusions	Enzalutamide significantly improved PFS compared with bicalutamide in patients with mCRPC.

Sourced from:

1. Shore N, Chowdhury S, Vilers A, Klotz L, Siemens D, Phung D, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol.* 2016;17:153–63.

Zytiga® Study 301

Journal/Year	*The New England Journal of Medicine,* 2011; *The Lancet Oncology*, 2012
Author(s)	de Bono, Logothetis C, Molina A, et al.; Fizazi K, Scher HI, Molina A, et al.
Title	Abiraterone and increased survival in metastatic prostate cancer. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study
Study Design	Phase 3, multinational, double-blind, randomized placebo-controlled trial
Patient Population Studied	• 1195 men with mCRPC progressing after docetaxel
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Men with histologically or cytologically confirmed mCRPC • Previous treatment with docetaxel • ≤ 2 previous chemotherapies • Disease progression (defined as two consecutive increases in the PSA concentration over a reference value) or radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value • ECOG performance status score of ≤2 • Ongoing ADT to maintain serum testosterone concentration <50 ng/dL • Hematology and chemistry laboratory values that met predefined criteria Exclusion: • Patients with mCRPC with neuroendocrine differentiation • Abnormal aminotransferase levels • Serious coexisting nonmalignant disease • Active or symptomatic viral hepatitis or chronic liver disease • Uncontrolled hypertension • History of pituitary or adrenal dysfunction • Clinically significant heart disease • Previous progression on ketoconazole
Treatment Arm	Abiraterone acetate (1000 mg; four tablets of 250 mg QD) + prednisone (5 mg tablet, BID)
Comparator Arm	Placebo (four tablets) QD + prednisone (5 mg tablet, BID)
Primary Endpoint(s)	OS
Secondary Endpoint(s)	• PSA response rate (proportion of patients with a decrease in PSA ≥50% from baseline, which was confirmed ≥4 weeks later by an additional PSA evaluation) • Time to PSA progression (TTPP) • Radiographic progression-free survival

Efficacy Outcomes	• The median duration of follow-up was 12.8 months at the time of data cutoff for the preplanned interim analysis; in the interim analysis, the overall median survival was longer in the abiraterone acetate plus prednisone group than in the placebo–prednisone group (14.8 months vs 10.9 months; HR = 0.65; 95% CI: 0.54 to 0.77; *P* < 0.001). • An updated survival analysis that was performed at median follow-up of 20.2 months found that the median OS for the abiraterone acetate plus prednisone group was 15.8 months (95% CI: 14.8 to 17.0) compared with 11.2 months (95% CI: 10.4 to 13.1) in the placebo plus prednisone group; (HR = 0.74; 95% CI: 0.64 to 0.86; *P* < 0.0001) • All secondary endpoints, including time to PSA progression (10.2 months in the abiraterone acetate plus prednisone group vs 6.6 months in the placebo plus prednisone group; *P* < 0.001), rPFS (5.6 months in the abiraterone acetate plus prednisone group vs 3.6 months in the placebo plus prednisone group; *P* < 0.001), and confirmed PSA response on the basis of PSA concentration (29.1% in the abiraterone acetate plus prednisone group vs 5.5% in the placebo plus prednisone group, *P* < 0.001), favored the treatment group. • Secondary endpoints (ie, time to PSA progression, radiographic progression-free survival, and the proportion of patients with a PSA response) were improved with abiraterone acetate plus prednisone group compared with placebo plus prednisone group. Median time to PSA progression (8.5 months, 95% CI: 8.3 to 11.1, in the abiraterone acetate plus prednisone group vs 6.6 months, 95% CI: 5.6 to 8.3, in the placebo group; (HR = 0.63, 95% CI: 0.52 to 0.78; *P* < 0.0001), median radiologic progression-free survival (5.6 months, 95% CI: 5.6 to 6.5, vs 3.6 months, 95% CI: 2.9 to 5.5); (HR = 0.66, 95% CI: 0.58 to 0.76; *P* < 0.0001), and proportion of patients who had a PSA response (235 [29.5%] of 797 patients vs 22 [5.5%] of 398; *P* < 0.0001) were all improved in the abiraterone acetate plus prednisone group compared with the placebo plus prednisone group.
Selected Safety Data	The most common grade 3–4 AEs in the abiraterone acetate plus prednisone group vs placebo plus prednisone group were: • Fatigue • Anemia • Back pain • Bone pain Mineralocorticoid excess-related adverse effects were of special interest and included: • Fluid retention or edema • Hypokalemia • Adverse events of special interest included those associated with elevated mineralocorticoid levels due to CYP17 inhibition (fluid retention and edema, hypokalemia, and hypertension) as well as cardiac disorders and liver function test abnormalities • Hypertension Mineralocorticoid excess-related adverse effects, including hypokalemia, hypertension, and fluid retention, occurred more frequently in patients who received abiraterone acetate compared with patients who received placebo. These mineralocorticoid excess-related adverse effects were largely abrogated by the use of low-dose prednisone or prednisolone (5 mg twice a day).
Selected Treatment Discontinuation Data %	Patients in the abiraterone acetate plus prednisone group vs patients in the placebo plus prednisone group: • 105 (13%) of 791 patients vs 71 (18%) of 394 patients discontinued due to AEs • 73 (9%) patients vs 28 (7%) patients interrupted treatment due to serious AEs or admission to hospital
Summary of Authors' Conclusions	Abiraterone acetate + prednisone significantly prolongs OS in patients with mCRPC that has progressed after docetaxel treatment

Sourced from:

1. de Bono, Logothetis C, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *The New England Journal of Medicine*. 2011; 364(21):1995-2005.
2. Fizazi K, Scher HI, Molina A., et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13:983-992.

Zytiga® Study 302

Journal/Year	*New England Journal of Medicine*, 2013*; Lancet Oncology,* 2015
Author(s)	Ryan CJ, Smith MR, de Bono JS, et al; Ryan C, Smith M, Fizazi K, et al.
Title	Abiraterone in metastatic prostate cancer without previous chemotherapy Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study
Study Design	Phase 3, randomized, multinational, double-blind, placebo-controlled study
Patient Population Studied	• Progressive mCRPC without prior chemotherapy • Asymptomatic or mildly symptomatic
Selected Patient Inclusion/Exclusion Criteria	Inclusion: • Metastatic, histologically or cytologically confirmed adenocarcinoma of the prostate • No prior chemotherapy • Prostate-specific antigen (PSA) progression or radiographic progression in soft tissue with or without PSA progression • Ongoing ADT to maintain serum testosterone concentration <50 ng/dL • ECOG performance status score of 0 or 1 • BPI-SF scores of 0-1 (asymptomatic) or 2-3 (mildly symptomatic) • Previous anti-androgen therapy followed by documented PSA progression after discontinuing the anti-androgen Exclusion: • Visceral metastases or previous therapy with ketoconazole for ≥ 7 days
Treatment Arm	Abiraterone acetate 1000 mg (four 250 mg tablets) QD + prednisone 5 mg (orally) BID
Comparator Arm	Placebo (four tablets) QD + prednisone 5 mg (orally) BID
Co-Primary Endpoint(s)	Co-primary endpoints • rPFS • OS
Secondary Endpoint(s)	• Time to opiate use for cancer-related pain. • Time to initiation of cytotoxic chemotherapy • Time to a decline in ECOG performance status • Time to PSA progression

Efficacy Outcomes	• At the time of the first interim analysis of rPFS, conducted when 13% of deaths had occurred, there was a 57% reduction in the risk of radiographic progression or death in the abiraterone acetate + prednisone group (median not reached) compared with the placebo + prednisone group (median of 8.3 months) (HR = 0.43; 95% CI: 0.35 to 0.52; *P* < 0.001). At the time of the second interim analysis of rPFS, conducted when 43% of deaths had occurred, the median time to rPFS was 16.5 months in the abiraterone acetate + prednisone group and 8.3 months in the placebo + prednisone group (HR = 0.53; 95% CI: 0.45 to 0.62; *P* < 0.001). • At the time of the planned interim analysis of OS, the median duration of follow-up was 22.2 months. In the abiraterone acetate + placebo group, 186 of 542 patients (34%) died vs 147 of 546 patients (27%) of patients in the placebo + prednisone group (HR = 0.75, 95% CI: 0.61 to 0.93; *P* = 0.01). • At final analysis (median follow-up of 49.2 months), 741 (96%) of the prespecified 773 death events for the final analysis had been observed: 354 (65%) of 546 patients in the abiraterone acetate + prednisone group and 387 (71%) of 542 in the placebo group. 238 (44%) patients initially receiving prednisone alone subsequently received abiraterone acetate plus prednisone as crossover per protocol (93 patients) or as subsequent therapy (145 patients). Overall, 365 (67%) patients in the abiraterone acetate group and 435 (80%) in the placebo group received subsequent treatment with one or more approved agents. • Median overall survival was significantly longer in the abiraterone acetate group (34.7 months; 95% CI: 32.7 to 36.8) compared with the placebo group (30.3 months; 95% CI: 28.7 to 33.3); HR= 0.81; 95% CI: 0.70 to 0.93; *P* = 0.0033. • Compared with placebo + prednisone, treatment with abiraterone + prednisone significantly increased the median time to: decline in ECOG performance score by ≥1 point (12.3 months vs 10.9 months, respectively; HR = 0.82; 95% CI: 0.71 to 0.94; *P* = 0.005), initiation of cytotoxic chemotherapy (25.2 months vs 16.8 months, respectively; HR = 0.58; 95% CI: 0.49 to 0.69; *P* < 0.001), PSA progression (11.1 months vs 5.6 months, respectively; HR = 0.49, 95% CI: 0.42 to 0.57; *P* < 0.001). At final analysis, the median time to opiate use was significantly longer in patients treated with abiraterone acetate + prednisone (33.4 months; 95% CI: 30.2 to 39.8) compared with patients treated with placebo + prednisone (23.4 months; 95% CI: 20.3 to 27.5); HR = 0.72; 95% CI: 0.61 to 0.85; *P* < 0.0001. • The effect of abiraterone acetate was consistent across all prespecified subgroups.
Selected Safety Data	At a median follow-up of 22.2 months, the most common grade 3–4 adverse events of special interest were: • Cardiac disorders (31 [6%] of 542 patients in the abiraterone acetate + prednisone group vs 18 [3%] of 540 patients in the placebo group) • Increased alanine aminotransferase (29 [5%] patients in the abiraterone acetate + prednisone group vs 4 [<1%] patients in the placebo group) • Hypertension (21 [4%] patients in the abiraterone acetate + prednisone group vs 16 [3%] patients in the placebo group) At final analysis, grade 3 or 4 AEs were reported in 54% and 44% of patients in the abiraterone acetate plus prednisone group and placebo plus prednisone group, respectively. Grade 3 or 4 adverse events of special interest were: • Cardiac disorders (41 [7%] of 542 patients in the abiraterone acetate + prednisone group vs 20 [4%] of 540 patients in the placebo group) • Increased alanine aminotransferase (32 [6%] patients in the abiraterone acetate + prednisone group vs four [<1%] patients in the placebo group) • Hypertension (25 [5%] patients in the abiraterone acetate + prednisone group vs 17 [3%] patients in the placebo group)
Selected Treatment Discontinuation Data	At final analysis, AEs leading to treatment discontinuation were reported in 13% and 10% of patients in the abiraterone acetate plus prednisone group and placebo plus prednisone group, respectively. The most common reason for discontinued treatment was disease progression (366 [68%] patients in the abiraterone acetate + prednisone group and 370 [69%] in the placebo group); adverse events were the second most common reason (50 [9%] abiraterone acetate + prednisone and 33 [6%] placebo group). Drug-related adverse events leading to treatment discontinuation occurred in 35 (7%) of 542 patients in the abiraterone acetate + prednisone group and 23 (4%) of 540 patients in the placebo group.
Summary of Authors' Conclusions	• Interim analyses showed that abiraterone acetate improved rPFS, showed a trend toward improved OS, and significantly delayed clinical decline and initiation of chemotherapy in patients with mCRPC • At a median follow-up of more than 4 years, statistically significant improvement in OS was observed with abiraterone acetate, by a margin that was both clinically and statistically significant [• Abiraterone acetate delayed onset of symptoms and need for opiate analgesics (HR= 0.72; 95% CI: 0.61 to 0.85; *P* < 0.0001)

Sourced from:

1. Ryan C, Smith M, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2015; 16:152–60.
2. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *New Engl J Med*. 2013;368:138-48.

Abbreviations

ADT = androgen-deprivation therapy

BID = twice daily

BPI-SF = Brief Pain Inventory-Short Form

CI = confidence interval

CRPC = castration-resistant prostate cancer

ECOG = Eastern Cooperative Oncology Group

HR = hazard ratio

IQR = interquartile range

LHRH = luteinizing hormone-releasing hormone

mCRPC = metastatic castration-resistant prostate cancer

OS = overall survival

PFS = progression-free survival

PSA = prostate-specific antigen

QD = once a day

RECIST = Response Evaluation Criteria in Solid Tumors

rPFS = radiographic progression-free survival