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Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer

Maha Hussain, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Per Rathenborg, M.D., Neal Shore, M.D., Ubirajara Ferreira, M.D., Ph.D., Petro Ivashchenko, M.D., Eren Demirhan, Ph.D., Katharina Modelska, M.D., Ph.D., De Phung, B.S., Andrew Krivoshik, M.D., Ph.D., and Cora N. Sternberg, M.D.

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RobotReviewer report

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
MH, 2018	RCT	626	+	?	+	+

Characteristics of studies

MH, 2018

Population	1. METHODS In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic , castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 2. CONCLUSIONS Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo. 3. In each trial group, the incidence of major adverse cardiac events was higher among patients who had a history of cardiovascular disease, hypertension, diabetes mellitus, or hyperlipidemia at baseline or who were 75 years of age or older than among patients without those charac- teristics.
Intervention	1. METHODS In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic , castration-resistant prostate cancer and a PSA doubling time

	of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 2. Patients were stratified according to the PSA doubling time (<6 months vs. ,â•6 months) and previous or current use of a bone-targeting agent at baseline (yes vs. no) and were randomly assigned in a 2:1 ratio to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 3. CONCLUSIONS Among men with nonmetastatic, castration-resistant prostate cancer with a rapidly rising PSA level, enzalutamide treatment led to a clinically meaningful and significant 71% lower risk of metastasis or death than placebo.
Outcomes	1. The primary end point was metastasis-free survival (defined as the time from randomization to radiographic progression or as the time to death without radiographic progression). 2. Secondary end points included the time to PSA progression, the PSA response rate (on the basis of a decrease from baseline of ,â•50%), the time to the first use of a subsequent antineoplastic therapy, quality-oflife assessments, overall survival, and safety. 3. Key secondary end points of the time to PSA progression and the time to the first use of a subsequent antineoplastic therapy and the first interim analysis of overall survival were evaluated at the time of the primary analysis.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Patients were stratified according to the PSA doubling time (<6 months vs. ,â•6 months) and previous or current use of a bone-targeting agent at baseline (yes vs. no) and were randomly assigned in a 2:1 ratio to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 2. METHODS In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic , castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 3. The trial groups were compared with the use of a log-rank test with stratification according to the same factors that were used in randomization .
Allocation concealment	high/unclear	1. The PSA level was assessed at a central laboratory; investigators and patients were unaware of the PSA values. 2. The trial regimen was continued until radiographic progression , as assessed by central independent blinded radiographic review. 3. METHODS In this double-blind, phase 3 trial, we randomly assigned, in a 2:1 ratio, men with nonmetastatic , castration-resistant prostate cancer and a PSA doubling time of 10 months or less who were continuing androgen-deprivation therapy to receive enzalutamide (at a dose of 160 mg) or placebo once daily.
Blinding of participants and personnel	low	1. The PSA level was assessed at a central laboratory; investigators and patients were unaware of the PSA values. 2. Patients were stratified according to the PSA doubling time (<6 months vs. ,â•6 months) and previous or current use of a bone-targeting agent at baseline (yes vs. no) and were randomly assigned in a 2:1 ratio to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 3. We conducted PROSPER, an international, doubleblind , randomized, placebo-controlled, phase 3 trial, which was approved by the independent review board at more than 300 sites in 32 countries .

Blinding of outcome assessment	low	1. Patients were stratified according to the PSA doubling time (<6 months vs. ,â•6 months) and previous or current use of a bone-targeting agent at baseline (yes vs. no) and were randomly assigned in a 2:1 ratio to receive enzalutamide (at a dose of 160 mg) or placebo once daily. 2. The data analyses reported here were performed by the sponsors and were provided to all the authors, who wrote the manuscript and made the decision to submit it for publication. 3. The PSA level was assessed at a central laboratory; investigators and patients were unaware of the PSA values.