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RESEARCH HIGHLIGHT

Prostate Cancer

Enzalutamide: a new indication for nonmetastatic castration-resistant prostate cancer

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PROSPER is an international Phase III trial demonstrating the beneficial role of enzalutamide, an androgen receptor antagonist, in prolonging metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer. The trial showed that the median metastasis-free survival was 21.9 months longer for those treated with enzalutamide (36.6 months) compared to those treated with placebo (14.7 months). Enzalutamide also showed prolonged time to PSA progression, PSA response, and time to initiating additional antineoplastic therapy although overall survival is not yet reached. Enzalutamide is the second antiandrogen (next to apalutamide) that has gained the United States Food and Drug Administration (US FDA) label indication for use in the setting of nonmetastatic castration-resistant prostate cancer.

Prostate cancer remains the most common noncutaneous cancer among American men. While majority of prostate cancer is cured, a subset of patients will relapse with biochemical recurrence for whom treatment with androgen deprivation therapy (ADT) is used in the United States. While treatment with ADT is often effective, castration resistance ultimately ensues and the state of nonmetastatic castration-resistant prostate cancer (nmCRPC) was an area of prostate cancer for whom few treatment options existed before novel antiandrogens showed promise. Apalutamide was one of the first antiandrogens that recently garnered US FDA approval in this space in a similarly designed trial called SPARTAN.[1] More recently, enzalutamide also was approved based on a Phase III randomized trial called PROSPER.[2]

PROSPER is a Phase III, double-blind, randomized, placebo-controlled international trial that utilized enzalutamide, an antiandrogen that has already shown to improve overall survival in different disease states of metastatic castration-resistant prostate cancer postdocetaxel in the AFFIRM[3] trial as well as in the predocetaxel trial called PREVAIL.[4] Other trials evaluating enzalutamide in different disease states comparing it to bicalutamide have also shown promise. PROSPER was conducted in over 300 sites in 32 countries and involved 1401 patients. The study required 440 metastasis-free survival events to have 90% power to detect a hazard ratio of 0.72. Entry eligibility criteria included patients who were at high risk for developing metastases, which includes a rising PSA level despite castrate levels of testosterone with a PSA doubling time (PSADT) of 10 months or less, no evidence of metastatic disease on conventional scans, at least a PSA level of 2 ng ml^{-1}, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients were randomized in a 2:1 fashion to receive either enzalutamide plus continued ADT versus placebo plus. Patients were further stratified into groups based on PSADT of <6 months versus 6–10 months and whether they were already receiving treatment with a bone-targeted agent. Patients in both treatment groups were similar at baseline in terms of age, ECOG performance, median serum PSA levels and doubling times as well as the use of a bone-targeting agent. The median PSA was around 10 ng ml^{-1} with a short median PSADT of 3.7 months.

The primary endpoint of the trial was metastasis-free survival (MFS), which was based on radiographic progression at any time or death within 112 days of suspending treatment. The study did meet its primary endpoint, showing that enzalutamide resulted in a median MFS of 36.6 months compared to 14.7 months for those who received placebo, translating to a statistically significant relative risk reduction of 71% in disease progression or death. Data collection was terminated when 447 MFS events were reached at which point only 634 patients were receiving enzalutamide and 176 patients were receiving placebo. Secondary endpoints were also in favor of those receiving enzalutamide with a statistically significantly longer time to PSA progression of 37.2 months compared to 3.9 months in the placebo cohort. Time to first use of a subsequent antineoplastic agent was also significantly longer in those receiving enzalutamide (median: 39.6 months) versus placebo (median: 17.7 months). Reassuringly, there was no significant difference between the groups in terms of quality of life. Data for median overall survival has not yet been reached in either arm, and no statistically significant advantage to overall survival was seen for either group. At the time of initial analysis, 103 of 933 patients (11%) in the enzalutamide group had died compared to 62 of 469 patients (13%) in the placebo group. However, death without documented disease progression that occurred within 112 days after discontinuation of treatment was seen in 15% of patients in the enzalutamide arm compared to 2% in the placebo arm,[5] though no real trends regarding cause of death were further elucidated and most of the deaths were deemed by investigators to be unrelated to the trial regimen.

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These results herald the utility of enzalutamide for another phase of disease of prostate cancer that is the nm CRPC space. For the enzalutamide group, there was a significantly increased MFS time compared to placebo of approximately 22 months. It should be noted that this marks one of the first times that the US FDA has granted drug approval based on this surrogate endpoint. MFS as an endpoint allows for an expeditious evaluation of new treatment options, especially since longer periods of time may be needed to fully await effects of treatment on survival outcomes.[6,7] Of note, earlier studies using denosumab which yielded a median 4-month improvement in MFS did not garner the same FDA approval.[8] On the other hand, enzalutamide already has shown strong precedence with survival effects in both the mCRPC patient population of postdocetaxel and predocetaxel arms as seen in the AFFIRM and PREVAIL trials, respectively.

Secondary endpoints also mostly favored the enzalutamide group with significant benefits of therapy in the median time to PSA progression which was 37.2 months for the enzalutamide group versus 3.9 months for the placebo arm and the PSA response rate with confirmed PSA response of ≥50% occurring in 76% of the patients who received enzalutamide versus 2% in the placebo arm. These results are expected given the known beneficial effects of enzalutamide on the androgen pathway. Patients who were started on enzalutamide also had a decreased need for subsequent antineoplastic therapy with a median delay in the first initiation of subsequent therapy at 39.6 months for the enzalutamide arm versus 17.7 months for those who received placebo. Furthermore, once the trial regimen was discontinued, the subsequent antineoplastic therapy was most commonly abiraterone in both groups.

Unsurprisingly, adverse events were more common in the enzalutamide group compared to placebo. Fatigue was the most prevalent adverse event and was known to occur at a rate of approximately 33% in patients taking enzalutamide compared to 14% for those on placebo. Cardiovascular effects, especially hypertension, along with falls, were also seen as side effects of enzalutamide and these occurred in 12% versus 5% and 11% versus 4%, respectively, for the enzalutamide compared to the placebo groups. Seizures were a known side effect of enzalutamide in the mCRPC trials, and enzalutamide therefore is contraindicated in patients with a history of seizure disorder. The incidence of seizures was <1% in all patients who were on the enzalutamide arm in the PROSPER trial. Serious adverse events were more common in the enzalutamide group, including any adverse event that led to discontinuation of the trial regimen or leading to death. Serious adverse events included events that resulted in death, were life threatening, resulted in prolonged hospitalization, and resulted in inability to conduct normal life functions. Reassuringly, there was no significant advantage nor detriment for either group in Functional Assessment of Cancer Therapy-Prostate (FACT-P) score, certainly comforting to know since one of the concerns arising out of the earlier use of active antiandrogens is the overall effect on quality of life, especially if a subset of men were to be exposed further to the prolonged side effects of therapy.

While the primary endpoint was met and majority of the secondary endpoints did favor enzalutamide use, the median overall survival has not yet been reached in either group. Of the thirty-two deaths without evidence of radiographic progression of disease that occurred in the enzalutamide group, only two were considered to be related to enzalutamide as per the investigators, including hemorrhagic ulcer and general physical health deterioration. Eleven of the deaths were considered to be cardiovascular in nature, and half of these patients had a prior history of cardiovascular disease, highlighting the need to further optimize cardiovascular risk factors while on antiandrogen and ADT. Further, safety analyses of the subgroups are currently ongoing. Ultimately, it would be important to determine whether MFS in this population of patients will translate to overall survival, which will provide meaningful delay in emergence of symptoms and added overall benefit. In addition, determination of which agent to use, whether enzalutamide or the previously approved apalutamide, remains to be determined.

In conclusion, the findings of this trial support the use of enzalutamide for men who have nmCRPC, and the PROSPER data have led to the United States FDA approval for enzalutamide for the treatment of men with nmCRPC on July 2018.

COMPETING INTERESTS

JBAC has previously served in the Speakers' Bureau of Astellas/Medivation and has served in the Advisory Board for Janssen. LPR and BG have no conflicts to disclose.

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