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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Further analysis of PREVAIL: enzalutamide use in chemotherapy-naïve men with metastatic castration-resistant prostate cancer

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PREVAIL was a phase III multinational, double-blind, placebo-controlled trial that enrolled chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC), which showed remarkable improvement in co-primary endpoints with an overall 81% reduction in the risk of radiographic progression, as well as 29% reduction in the risk of death in favor of the enzalutamide arm over placebo. All secondary endpoints including time to subsequent chemotherapy initiation and prostate specific antigen (PSA) progression were in favor of the enzalutamide arm. The results of PREVAIL shows the utility of enzalutamide that would likely soon expand the indication to asymptomatic or minimally symptomatic men with mCRPC not previously treated with chemotherapy.

Enzalutamide is a second-generation oral androgen-receptor (AR) inhibitor that was first approved by the United States Food and Drug Administration labeled for use in men after failure of docetaxel in a phase III study coined the AFFIRM trial.[1] PREVAIL comes at the heels of the AFFIRM trial, enrolling 1717 men with mCRPC who were chemotherapy-naïve and who have failed standard hormonal therapy.[2] This multinational trial was conducted in a double-blind, placebo-controlled, randomized 1:1 fashion with co-primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) with an intention-to-treat analysis. The findings showed a remarkable improvement in both primary endpoints with an rPFS median of not reached in the enzalutamide arm versus only 3.9 months in the placebo at about 12 months of follow-up, which translated to 81% reduction in the risk of radiographic progression with a rate of rPFS at 65% in the enzalutamide group versus 14% in the placebo group at the same time-frame. Similarly, OS at a median follow-up of 22 months showed more deaths occurring in the placebo arm at 35% versus 28% in the enzalutamide arm, translating to a 29% decreased risk of death (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.60–0.84; $P < 0.001$). Furthermore, the updated analysis showed that the estimated median OS was not yet reached for the enzalutamide arm versus 31 months in the placebo (HR, 0.73; 95% CI, 0.63–0.85, $P < 0.001$). All the secondary and exploratory prespecified endpoints were statistically significant ($P < 0.001$) and in favor of the enzalutamide arm over placebo, including the median time to initiation of chemotherapy with 28 months versus 10.8 months, median time to decline in the quality of life scores at 11.3 versus 5.6 months, the median time to PSA progression at 11.2 versus 2.8 months and objective responses of 59% versus 5%, respectively. The use of enzalutamide in this prechemotherapy population of men was also deemed safe with fatigue, back pain, arthralgias, and constipation as the most common adverse events occurring in 20% or more of patients in the enzalutamide group. In general, a higher rate of events that included hot flushes, falls and hypertension occurred in the enzalutamide compared to the placebo arm, especially after adjustment of time to exposure since there was a longer period of adverse event reporting with enzalutamide at 17.1 months compared to only 5.4 months in the placebo group, and hypertension occurred as the single most common grade 3 event or higher in 7% of patients. Of interest is the reporting of only one seizure event in both the enzalutamide and the control group, as opposed to the seven patients reported in the AFFIRM trial,[1] most of whom had some predisposing factor for lowering the seizure threshold.

The PREVAIL trial showed unprecedented results in the contemporary era of treatment of mCRPC patients. The patient population treated in PREVAIL closely mimics another pre-chemotherapy group of patients seen in the COU-AA-302 trial that utilized abiraterone acetate with prednisone,[3] and even the IMPACT trial utilizing sipuleucel-T although some 15%–19% of patients with prior receipt of chemotherapy was allowed in the latter trial.[4] The PREVAIL trial showed that men on enzalutamide had delayed chemotherapy administration by a median of 17 months, compared to only 8 months in the COU-AA-302 trial. However, it should be noted that the abiraterone 302 trial used prednisone as the comparator arm, rather than placebo, which was used in the PREVAIL arm, which could render some modest responses in and of itself as seen in historical controls where prednisone was typically used as the comparator treatment arm.[5] In addition, while the 302 trial showed a 25% decrease in the risk of death for the experimental abiraterone with prednisone arm, the OS did not reach the prespecified statistical boundary of significance albeit the rPFS was statistically different with a 57% reduction in risk of progression with updated analysis of median rPFS of 16.5 months in the abiraterone-prednisone group compared to 8.3 months

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in the prednisone-placebo group. Another notable difference between the PREVAIL and COU-AA-302 trial included enrollment of patients with visceral disease in 11.2% of enzalutamide patients in the PREVAIL study, while none was allowed in the 302 trial. Both trials essentially excluded prior receipt of ketoconazole except if <7 days in the 302 trial.

The burgeoning question given the positive results of the PREVAIL trial is the appropriate sequencing or combination of these agents, especially where it relates to the use of androgen-targeted signaling inhibitors. It is conceivable that the disease biology and patterns of resistance change as patients receive one agent over another in a particular sequence. For instance, the response rates and survival as reported in the pivotal AFFIRM trial may not recapitulate what is seen in actual practice given prevalent use of abiraterone acetate in North America because of preceding approval of abiraterone for chemotherapy-naïve men with mCRPC. Indeed, in a small 35-patient study looking at responses to enzalutamide post-docetaxel and abiraterone failure, majority (71.4%) of men did not achieve a PSA decline of >50% indicating high rates of resistance in this group of patients.[6] Emerging reports of cross-resistance to varying agents are also increasingly identified,[7] with recognition that taxanes may also act to inhibit AR translocation through association of tubulin to the AR.[8] To this end, studies looking at mechanisms of resistance and use of different molecular techniques such as interrogating the presence of AR splice variants that effectively truncate the ligand-binding domain that is essential for enzalutamide binding, can shed light on further development of newer generation AR signaling agents to overcome this resistance.[9] Issues and limitations surrounding choice of clinical trial endpoints are also increasingly recognized since newer generations of novel anti-androgens or androgen-signaling inhibitors such as TAK-700, which while potentially more potent, has difficulty demonstrating OS benefits as seen in the recent results of the ELM-PC4 phase III trial[10] which has very similar entry criteria and endpoints as PREVAIL and COU-AA-302, yet did not meet the co-primary OS endpoints perhaps given dilution of effects from the landscape of multiple drugs that now yield OS benefits in this disease state.

The findings of PREVAIL certainly herald another landmark win for the treatment of mCRPC but continued efforts toward expanding the knowledge or understanding the mechanisms of resistance to these drugs and further evaluating the existing clinical trial endpoints are needed in order to keep bringing forth novel agents to the clinic remain as a tangible goal.

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