PROSTATE CANCER

Enzalutamide PREVAILS

Interim analysis of the PREVAIL trial, demonstrating the superiority of enzalutamide over placebo for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC), has now been published in *The New England Journal of Medicine*. The study data demonstrate that enzalutamide not only significantly improves survival outcomes, but also delays the need for chemotherapy, reduces serum PSA levels and is associated with better health-related quality of life.

This won't be the first you've heard of PREVAIL (NCT0121299), the double-blind phase III randomized controlled trial of enzalutamide versus placebo in the prechemotherapy setting that was halted early owing to overwhelming response to treatment. 1,717 men with mCRPC who had not previously received chemotherapy were recruited at 207 sites around the world between September 2010 and September 2012. Patients were randomized to receive a daily dose of either enzalutamide ($n=872$) or placebo ($n=845$). Co-primary end points were overall survival and radiographic progression-free survival.

The planned interim analysis of overall survival was performed in September 2013 after 540 deaths had occurred. At this point—median follow-up duration 22 months—enzalutamide was associated with a 29% reduced risk of death compared with placebo (hazard ratio [HR] 0.71, 95% CI 0.60–0.84; $P<0.001$). Radiographic progression-free survival at 12 months was 65% for patients who received enzalutamide and 14% for those in the placebo group, corresponding to an 81% risk reduction (HR 0.19, 95% CI 0.15–0.23; $P<0.001$). Based on these positive results, the study was unblinded and patients in the placebo group were given the opportunity to crossover to the enzalutamide arm.

“The most impressive findings are simply having achieved significant improvements in both co-primary end

points given the availability of multiple effective options that the control arm was able to access that could have eliminated any chance of seeing an overall survival advantage,” explains Fred Saad, one of the study investigators. Indeed, 40% and 70% of men in the enzalutamide and placebo groups, respectively, received subsequent cancer treatments, the most common agents being docetaxel (by 33% and 57% of patients, respectively) and abiraterone (by 21% and 46% of men, respectively).

The survival benefit of enzalutamide was apparent in all prespecified subgroups, including patients with visceral metastases in the lung or liver. “Although this represents a small group of patients, it is encouraging that the dogma that visceral metastases should always be treated with chemotherapy might be challenged,” Saad told *Nature Reviews Urology*.

However, there's much more to these data than just the survival outcomes. “In my opinion, some of the most exciting results are the tumour response findings,” says Saad. “Almost 60% partial or complete response in measurable lesions [for enzalutamide] is the best we have ever seen in mCRPC and clearly shows very effective anti-cancer activity.” Partial or complete response was reported in 5% of patients in the placebo group.

Other secondary end points included median time to initiation of chemotherapy (28 months versus 10 months; HR 0.35, 95% CI 0.30–0.40; $P<0.001$) and time to PSA progression (11.2 months versus 2.8 months; HR 0.17, 95% CI 0.15–0.20; $P<0.001$). “The PSA response is striking in this patient population,” says Saad. “We might criticize PSA, but patients and their treating physicians are very attached to this marker. Now, we can say that for enzalutamide, PSA is truly a valuable marker that correlates very well with radiological and clinical outcome measures.”

Health-related quality of life was also significantly better for patients who took enzalutamide. Median time

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to deterioration, according to the FACT-P scale, was 11.3 months for the enzalutamide arm and 5.3 months for patients who received placebo (HR 0.63, 95% CI 0.54–0.72; $P<0.001$).

Now that the advantages of enzalutamide have been demonstrated in mCRPC, attentions are turning to earlier stages of prostate cancer. Current goals include the evaluation of whether the drug can delay metastasis in patients with nonmetastatic high-risk disease or postpone progression to castration resistance over androgen deprivation therapy (ADT) in men with hormone-sensitive prostate cancer. “We now have evidence that patients with newly diagnosed metastatic disease have a significant overall survival advantage if chemotherapy is given upfront, so it would be valuable to know whether enzalutamide and other nonchemotherapeutic agents can also improve on ADT,” explains Saad. “There's lots of work left to do.”

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Original article Beer, T. M. *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* doi:10.1056/NEJMoa1405095

Further reading Payton, S. Enzalutamide impresses in European studies. *Nat. Rev. Urol.* 11, 243 (2014)