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To treat or not to treat: Weighing the evidence

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In this issue of JAMA Oncology, Shore et al. [1] present the results of the randomized phase II trial: the ENzalutamide Monotherapy Versus ACTive Surveillance in Patients With 2 Low- or Intermediate-Risk Localized Prostate Cancer (ENACT). Between June 2016 and August 2020227 men with prostate cancer were randomized with equal probability to either enzalutamide or active surveillance. The median age at randomization was 65 years and 53% of patients had low risk as determined by the National Comprehensive Cancer Network (NCCN) guidelines.[2] Patients on the treatment arm were treated with 160 mg enzalutamide for 1 year with initial follow up for 1 year and a second year of follow up for remaining patients in the trial. The primary endpoint was time to pathological or therapeutic prostate cancer progression. Pathological progression in the study was defined as an increase in primary or secondary Gleason pattern by at least one or higher proportion of cancer-positive cores (≥15% increase). Therapeutic progression was considered upon primary therapy for prostate cancer whether this was prostatectomy, radiation, focal therapy, or any systemic therapy.

Patients on the EN arm had a 46% lower hazard ratio of progression than patients on the active surveillance and this decrease was statistically significant. The median time to pathological or therapeutic progression was not reached in either arms. The incidence of pathological or therapeutic prostate cancer progression at 1-year was lower with enzalutamide, however no differences were observed at 2 years. In a subgroup analysis in patients with a Gleason score of 7, the median time to prostate cancer progression was not reached in the EN arm compared with 30 months in with AS.

Other secondary endpoints considered were the odds of negative biopsy, proportion of negative biopsy, time to PSA progression, and various patient reported outcomes (PRO). The proportion of negative biopsy was lower in the EN compared to the AS arms. Moreover, time to PSA progression was longer in enzalutamide versus AS. The authors assessed several PRO outcomes, such as the Brief Fatigue Inventory, 12-item Short Form Survey, Expanded Prostate Cancer Index Composite, and the Memorial Anxiety Scale for Prostate Cancer. Enzalutamide was associated with worsening of sexual and physical function. This was resolved by month 24 after treatment ended. Of note, only 74.6% of men in the EN arm

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and 70.8% of men in the AS arm completed 1 year of trial participation, highlighting one of the challenges of active surveillance protocols.

Enzalutamide is a potent inhibitor of the androgen receptor with a 5- to 8-fold greater binding affinity than bicalutamide which also inhibits AR translocation to the nucleus and binding to DNA and coactivators[3]. The clinical activity of enzalutamide is well documented in the advanced disease setting. A decrease in the size of the tumor, a lowering of the PSA and delaying the rise in the PSA would expectedly lead toward reduced risk of prostate cancer progression, improved odds of a negative biopsy, reduced the percentage of cancer-positive cores and decreased the rise in serum PSA at 1 year. This would be a predictable outcome for this class of agents. It is interesting that on the cessation of EN, the differences in the two arms at year 2 seemed to be very similar suggesting that the natural history of the tumor may not have been altered but patients on the EN arm had different growth kinetics while on active EN treatment. Whether this will translate into significantly delaying or abrogating the need for definitive therapy for a cohort of patients will require longer follow-up.

While the NCCN guidelines support the option of active surveillance in cases of low or intermediate risk for prostate cancer, the bigger question is whether the risk-benefit profile in these patients necessitates treatment with EN or another drug. A recent meta-analysis of over 6,700 men showed a 99.8 cancer specific survival at 6.7 years of follow up, with a 0.4% rate of systemic progression[4], values that are similar to other AS cohorts. These men in general will do well if followed closely. Patients with low and intermediate prostate cancer choose active surveillance to avoid harmful effects from the surgical or radiotherapy intervention; however let us be clear: EN is a systemic therapy to treat the cancer which was associated with decreased sexual and physical function in this study, however these were reversible unlike some long term side effect from surgery or radiotherapy.

So is the use of EN an alternative treatment option for men with low or intermediate risk prostate cancer? While the data are encouraging, unfortunately the trial falls short in identifying those particular patients that will have a clinical benefit from early systemic intervention with EN. It is critical that low- or intermediate risk prostate cancer patients be followed for at least a decade with studies sufficiently powered to detect those differences in outcomes in various subsets of patients.

It is also important to highlight that the primary endpoint of time to pathological or therapeutic prostate cancer progression has been used previously in the REDEEM trial in this patient population[5]. This is relatively a new composite endpoint that considers both pathological and therapeutic progression. But the problem of choosing appropriate endpoints in more indolent clinical situations remains elusive. Further studies are needed to evaluate whether this endpoint might translate to clinical benefit to the patients.

It is also not clear whether early usage of these type agents may reduce the effectiveness of enzalutamide or other similar agents' usage in future settings. While the risk may be small in the localized setting, activating androgen receptor mutations are indeed present in more advanced states of diseease[6]. Another notable concern for the patients could be the cost and

financial toxicity associated with such agents, as wholesale pricing for these agents runs well over $150,000 per year on treatment, although these costs would likely vary based on insurance coverage.[7] This, however, raises the point of what is the cost-benefit threshold for a treatable issue or solely to delay definitive therapy. While this data highlights a decreased risk in progression of prostate cancer in some patients on active surveillance, it raises many questions, particularly concerning the selection of those patients most likely to benefit from EN and appropriate endpoints to make that judgement. We look forward to additional data on this important and timely topic.

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