Re: Enzalutamide with Standard First-line Therapy in Metastatic Prostate Cancer

Davis I, Martin AJ, Stockler MR, et al.

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Experts' summary:

An open-label, phase 3 trial (ENZAMET) was performed in 1125 patients with metastatic hormone-sensitive prostate cancer (mHSPC) [1]. Patients were randomised 1:1 to receive continuous androgen deprivation therapy (ADT) plus open-label enzalutamide (160 mg daily) or ADT plus a standard nonsteroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide). The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS) as determined via prostate-specific antigen (PSA) levels, clinical progression-free survival (cPFS), and adverse events. Treatment with enzalutamide was associated with significantly longer OS (hazard ratio [HR] 0.67, 95% confidence interval 0.52–0.86; $p = 0.002$) compared with standard care alone, and significantly better PFS (HR 0.39; $p < 0.001$), and cPFS (HR 0.40; $p < 0.001$). However, patients in the enzalutamide group had a higher incidence of adverse events including seizures, which occurred in 1% of patients. Furthermore, among those who received early docetaxel treatment, grade 2 peripheral sensory neuropathy was reported in 9% of the enzalutamide group, compared to 3% in the standard care group. The use of early docetaxel in addition to enzalutamide did not provide significant survival advantages over enzalutamide alone.

Experts' comments:

Publication of results from ENZAMET rounds off an extraordinary 4-yr period in the management of mHSPC [1]. With ADT alone having been the standard of care for decades and OS rates still disappointing despite advances in the management of metastatic castration-resistant PC [2], strategies to improve OS in mHSPC have remained a research priority [3]. Pivotal studies since 2015 have confirmed that approaches combining ADT with upfront docetaxel, abiraterone, and apalutamide [4–7] all improve OS when compared with ADT alone, and therefore combination strategies are rapidly becoming the standard of care for mHSPC. ENZAMET adds combination therapy with enzalutamide to this list of life-prolonging therapies, providing a truly impressive range of options for men with mHSPC.

ENZAMET is of note for a couple of reasons. First, this was an academic trial, led by the Australia and New Zealand Urogenital and Prostate (ANZUP) trials cooperative group, involving patients in Australia, Europe, and North America. In a field usually dominated by industry-led registration trials, it is most welcome to see an academic group design and complete this important practice-changing study. Second, as the protocol allowed for use of upfront docetaxel, which was planned for almost half of the patients, we now have data to guide us on the role of "triplet" therapy in mHSPC for the first time.

Therefore, we can make the following observations. First, it appears that combination therapy with enzalutamide benefits all-comers with mHSPC, regardless of the volume or location of their disease. Second, it appears that there is no significant advantage in combining docetaxel chemotherapy upfront with ADT over docetaxel alone. Furthermore, there is greater toxicity when adding docetaxel to enzalutamide, with peripheral neuropathy reported for 9% of patients receiving enzalutamide and docetaxel. While we await results from other prospective studies, our prediction is that the future will not include so-called triplet therapy. Third, enzalutamide (and apalutamide) appears to produce similar OS benefits to those observed in studies combining docetaxel upfront, or abiraterone and prednisone upfront. However, enzalutamide and apalutamide have the advantage of avoiding chemotherapy and the use of steroids; this is likely to be attractive for patients and clinicians alike, especially as these patients predominantly present in the offices of urologists at diagnosis.

For all of the above reasons, we believe that ADT combined with AR-targeted therapies such as enzalutamide and apalutamide is likely to become the preferred combination strategy for many patients with mHSPC.

Conflicts of interest: Declan G. Murphy has received reimbursement for participation in advisory boards and delivering lectures from Astellas Pharmaceuticals, Janssen Pharma, Bayer, Ipsen, Ferring, and AstraZeneca. The remaining authors have nothing to disclose.

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Re: Urodynamics Useless in Female Stress Urinary Incontinence? Time for Some Sense—A European Expert Consensus

Finazzi-Agrò E, Gammie A, Kessler TM, et al

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Experts' summary:
The routine use of urodynamics (UDS) in the management of female stress urinary incontinence (SUI) is a controversial topic that is widely debated. Evidence from two randomized controlled trials (RCTs) has indicated that UDS may not be a necessary step for uncomplicated cases of SUI [1,2]. Conversely, many other sources, such as extensive experience and observational studies, suggest that UDS might be helpful in clinical decision-making and facilitate appropriate patient counseling. The focus of this multidisciplinary group of UDS experts was to consider the role and value of UDS for female patients who are potential candidates for SUI surgery. A modified version of the Delphi method was used to reach a consensus viewpoint structured around five key questions. The authors were unanimous in stating the important role of UDS in female SUI that should not be eclipsed by the findings in two RCTs with several biases.

Experts' comments:
While UDS in patients with complicated characteristics should be considered mandatory before surgery, its use for the management of uncomplicated or "index" SUI forms is controversial. This reflects the lack of evidence on the role of preoperative urodynamic evaluation in improving outcomes from continence surgery in index patients.

In our opinion, UDS is an important tool in the hands of clinicians for collection of additional functional information that could guide the right therapeutic choice. A simple office-based evaluation is not sufficient to identify some relevant issues that only UDS can detect, such as voiding dysfunction in the absence of a significant postvoid residual urine volume, "asymptomatic" detrusor overactivity, or a urethral sphincter deficiency [3,4].

The well-conducted European expert consensus by Finazzi Agrò et al has the merit of identifying many factors that may have contributed to the increasing underuse of UDS in female SUI. Although the group was composed of experts who routinely use UDS in their clinical practice, they presented objective and evidence-based opinions.

However, the lack of a standardized definition of uncomplicated SUI might be a limitation of this consensus paper. Therefore, a possible question for panelists could be: What do you consider to be "uncomplicated patients"? In the literature, there is no agreement on the definition of uncomplicated SUI, in particular among the different international guidelines [5]. In this scenario, it is difficult to compare the different studies and recommendations available.

Conflicts of interest: The authors have nothing to disclose.

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