Androgen receptor pathway inhibitor combination in prostate cancer

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A recent Research Highlight published in *Nature Reviews Urology* (Fenner, A. Darolutamide combo is an ARASENSible option for mHSPC. *Nat. Rev. Urol.* https://doi.org/10.1038/s41585-022-00579-0 (2022)) that discusses the ARASENS study suggests that combined darolutamide and standard of care (SOC) of docetaxel plus androgen deprivation therapy (ADT) is a sensible option for patients with hormone-sensitive prostate cancer (HSPC)[1,2]. The article also draws conclusions from ENZAMET and the yet-to-be published PEACE-1 studies and contrasts their findings on overall survival (OS)[3,4].

I would urge caution with this interpretation of the study, owing to a lack of evidence. Notably, although both patient groups in ARASENS were allowed to receive subsequent androgen receptor inhibitors, none of the patients in the placebo group received darolutamide. Furthermore, previous studies have shown that OS benefit with darolutamide is greater than that of enzalutamide and apalutamide, especially in patients with a PSA doubling time (PSA-DT) of >6 months[5].

Indeed, the findings of ARASENS show that darolutamide improves OS in patients with HSPC and that it might improve OS more than other androgen pathway inhibitors, as previously demonstrated by ARAMIS and a meta-analysis[5,6]. However, ARASENS does not show that combined SOC and darolutamide improves survival when compared with sequential darolutamide. The ARASENS study group has not published their data regarding PSA-DT, making it even harder to determine whether combined SOC and darolutamide is indeed suitable and beneficial for all patients.

With regards to the discrepancy between ENZAMET and PEACE-1, it is again notable that ENZAMET allowed the placebo group to receive sequential enzalutamide and subsequently found no OS benefit in the ADT plus docetaxel plus enzalutamide group in their subgroup analysis, a finding and study design that are in sharp contrast to ARASENS. As expected, enzalutamide also has a benefit on progression-free survival (PFS), with a stronger effect observed when combined with docetaxel.

This outcome suggests that androgen pathway inhibitors have a survival benefit regardless of whether they are combined with docetaxel. Whether or not the magnitude of benefit is higher or lower with the combinatory nature is still unknown and unanswered by ARASENS. This point is paramount given the importance of optimal sequencing of available therapies for oncologists to maximize survival benefits and treatment-free periods.

Unfortunately, PEACE-1 has yet to make available its sequential systemic options for its participants and if not compared like-with-like as is the case in ARASENS, then the current OS benefit observed might simply be an effect of abiraterone, rather than the combinatory effect with SOC therapies.

I would, therefore, exercise caution in interpreting ARASENS and in choosing treatment combination options for patients with prostate cancer before further evidence is available.

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Competing interests
The author declares no competing interests.

Management of very young fetuses with LUTO

Thomas Kohl

I congratulate Capone and colleagues on their efforts to draft new guidelines for the management of fetal lower urinary tract obstruction (LUTO), which were published in *Nature Reviews Urology* (Capone, V. et al. Definition, diagnosis and management of fetal lower urinary tract obstruction: consensus of the ERKNet CAKUT-Obstructive Uropathy Work Group. *Nat. Rev. Urol.* **19**, 295–303 (2022))[1].

In this manuscript, the authors make some observations based on previous studies: a bladder diameter ≥15 mm in the first trimester of pregnancy suggests severe LUTO with little chance of spontaneous resolution[2]; the presence of anhydramnios early in the second trimester of pregnancy results in a fetal mortality rate close to 100%, and untreated fetal LUTO with an early onset (first or early second trimester of pregnancy) can lead to death in up to 80% of fetuses[1–4]; and a small window of opportunity for improved renal outcomes and survival exists (<6 weeks), as renal function gets lost progressively in fetuses with severe LUTO[5].

Abnormal dilation of the lower urinary tract or of developmentally related anatomical structures from severe urinary outflow obstructions have a prominent position and unmistakable appearance (an anechoic sphere) in the lower abdomen of the fetus and, therefore, can easily be detected in fetuses in the first and early second trimesters of pregnancy. However, the new guidelines[1] about LUTO management primarily focus on mid-gestation fetuses and provide no recommendations about how to best handle this early-gestation subgroup of fetuses with LUTO. Thus, the staging system that the authors propose as well as some of the European Reference Network for Rare Kidney Diseases (ERKNet) recommendations for prenatal definition, diagnosis and management of LUTO[1,6] do not fit the needs of the youngest and most severely affected fetuses.

The purpose of this Correspondence is, therefore, to raise awareness about the availability of intervention methods alternative to the use of double pigtail catheters, such as trimmed 6F-single pigtail catheters or stent shunts, which enable clinicians to perform vesico-amniotic shunt insertion in first and early second trimester fetuses with LUTO with improved safety and efficacy[7,8].