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].

Moreover, I propose a new management algorithm to deal with young fetuses with LUTO, who might most benefit from this procedure, developed and tested at the German Center for Fetal Surgery & Minimally-Invasive Therapy (DZFT - Mannheim, Germany)[7]. The proposed management technique is also less invasive for mothers and fetuses than previous strategies, as repeated punctures for karyotyping and serial collection of fetal urine before the actual shunt insertion are avoided.

The algorithm includes the following steps: treatment of fetuses with isolated severe LUTO within days from the first diagnosis (from as early as 12 weeks of gestation onward); karyotyping performed from amniotic fluid collected at the time of shunt insertion; avoidance of any treatment delays not waiting for oligohydramnios to occur; implementation of weekly follow-up monitoring over the remainder weeks of gestation; and re-intervention within days in the presence of shunt dislodgement, shunt malfunction or signs of additional severe bilateral upper urinary tract obstructions or urinary ascites[7].

Using this algorithm, 19 of 28 fetuses (68%) survived to postnatal discharge from hospital after a mean number of interventions of 1.6 per fetus (range 1–4)[7]. Overall, 15 of the 19 surviving fetuses (79%) had normal renal function, and pulmonary hypoplasia was present in only 2 fetuses (11%)[7]. These results reflect some of the best renal and pulmonary outcomes ever described following vesico-amniotic shunt insertion in a cohort of fetuses with LUTO.

Results from early vesico-amniotic shunt insertions in first or early second trimester fetuses with severe LUTO performed in our centre and by other groups[9,10] showed similarly encouraging outcomes. Considering the life-saving potential of this approach, I believe that this information needs to accompany the novel management guidelines for fetal LUTO[1].

After more than three decades of therapeutic stagnation in this corner of prenatal medicine, good evidence supports the idea that results from future studies will confirm that vesico-amniotic shunting before the completion of 16 weeks of gestation improves postnatal conditions of fetuses with LUTO. However, further follow-up studies are clearly needed to assess whether and for how long the improved renal and pulmonary outcomes observed in young fetuses with LUTO might persist.

There is a reply to this letter by Capone, V., Persico, N. & Montini, G. *Nat. Rev. Urol.* https://doi.org/10.1038/s41585-022-00637-7 (2022).

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Competing interests
The author declares no competing interests.

Reply to 'Management of very young fetuses with LUTO'

Valentina Capone, Nicola Persico and Giovanni Montini

We thank Thomas Kohl for his correspondence on our ERKNet Consensus Statement on prenatal LUTO (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]), which raises some important issues (Kohl, T. Management of very young fetuses with LUTO. *Nat. Rev. Urol.* https://doi.org/10.1038/s41585-022-00636-8 (2022)[2]). In our paper, we recommend offering prenatal intervention in fetuses with LUTO, as this approach increases perinatal survival (defined as survival at 6 months of age) compared with conservative management (57% versus 39%, respectively), with no evidence of effects on long-term mortality and kidney function. This recommendation is based on published literature reporting intrauterine treatment by vesico-amniotic shunt (VAS) placement at 20–27 weeks of gestational age in most studies[1]. We are aware of the importance of early treatment in the most severe instances, with the objective to improve kidney function. However, no sufficient evidence is available to make a recommendation on the optimal timing of prenatal intervention.

The study by Kohl and colleagues involves 28 fetuses with severe megacystis treated before 16 weeks' gestation[3]. In this study, very early treatment is associated with fetal loss in 9 of 28 instances (32%), with 4 demises after intervention and 5 terminations of pregnancy. Moreover, a high rate of post-natal complications is observed in survivors, including bowel atresia, vesico-cutaneous fistulas and bowel eventration.

Prenatal guidelines on invasive diagnostic testing recommend not to perform amniocentesis, which is carried out with a thinner needle than the devices used for VAS, before 15 weeks' gestation, owing to the high rate of chorioamniotic membrane separation and consequent rupture of membranes (grade A recommendation)[4]. Thus, further research should be carried out to investigate the safety and efficacy of VAS before 16 weeks, regardless of the device used.

The authors also report a normal kidney function in 15 of 19 survivors (79%). However, this evidence only refers to short-term kidney function based on serum creatinine at discharge from hospital, which is insufficient to define the long-term potential need of kidney replacement therapy for these children, as also underlined in a commentary article[5]. In a future consensus paper, finding an agreement on a common way to assess postnatal kidney function in children who underwent prenatal treatment, both in terms of age of follow-up visits and type of assessment will be crucial.

In conclusion, on the basis of current evidence, no recommendation can be made on very early prenatal treatment of LUTO, considering the high proportion of fetal demise and postnatal complications related to the procedure. Based on Kohl's data and