Disease volume and risk subgroup analyses for darolutamide plus androgen-deprivation therapy and docetaxel in the phase III ARASENS: should triplet therapy become standard of care in certain metastatic hormone-sensitive prostate cancer patients?

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The treatment for metastatic hormone-sensitive prostate cancer (mHSPC) has remarkably evolved in the last two decades due to various phase 3 randomized-controlled trials (RCT) demonstrating favorable overall survival (OS) outcomes for combination therapy of docetaxel as well as androgen receptor-axis-targeted therapy agent (ARAT) combined with androgen deprivation therapy (ADT) resulting in remarkable prolonged overall survival rates (1-8). In 2022, two RCTs (PEACE-1, ARASENS) demonstrated an overall survival benefit for triplet therapy [ARAT (PEACE-1: abiraterone; ARASENS: darolutamide) & docetaxel & ADT] over doublet therapy (docetaxel & ADT), thus, re-emphasizing the concept of early treatment intensification in mHSPC (8,9). However, bearing in mind that prior studies have indicated different extent of benefits for treatment intensification based on disease burden, data stratified according to disease burden is crucial when treatment decision are made in mHSPC. In contrast to the initial report of ARASENS in 2022 which did not include stratification according to disease burden, Hussain *et al.* performed in the current study a post hoc analysis of the ARASENS data investigating the effect of treatment intensification in mHSPC patients according to tumor burden. Specifically, the investigators reviewed efficacy (and safety) outcomes, focusing on OS in mHSPC patients stratified according to tumor volume and disease risk following CHAARTED (high-volume: visceral metastases and/or ≥4 bone metastases with ≥1 beyond the vertebral column/pelvis) and LATITUDE (high-risk: ≥2 risk factors: Gleason score ≥8, ≥3 bone lesions, visceral metastases) criteria, respectively (1,9). Here, Hussain *et al.* reported that triplet therapy increased overall survival OS versus docetaxel & ADT in patients with high-volume [hazard ratio (HR), 0.69; 95% CI: 0.57 to 0.82], high-risk (HR, 0.71; 95% CI: 0.58 to 0.86), and low-risk disease (HR, 0.62; 95% CI: 0.42 to 0.90), respectively (10). The current post hoc analysis by Hussain *et al.* contributes substantially to understand which mHSPC patients will likely benefit from a treatment intensification in terms of triplet therapy. It is of note that doublet therapy consisting of docetaxel & ADT, which was used in both ARASENS and PEACE-1 as standard of care, was superseded by doublet therapy consisting of ARAT and ADT, demonstrating more favorable survival outcomes with less toxicity (11-13).

As a consequence, questions arise whether triplet therapy will be more effective than doublet therapy consisting of ARAT & ADT. Since there are no direct comparison between triplet and doublet therapy (ARAT & ADT), decision making will most likely be driven by indirect comparisons and patient-characteristic based considerations

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resulting in various network meta-analyses investigating this question in the recent past (10-14). In our updated network meta-analysis, incorporating most recent data by Hussain *et al.* and grouping patients according to CHAARTED criteria, in high-volume mHSPC, triplet therapy (ARAT: darolutamide) ranked first and demonstrated a statistically significant overall survival benefit compared to doublet therapy consisting of ARAT & ADT (14). In contrast, in low-volume mHSPC patients, no statistical difference in OS was recorded for triplet therapy relative to ARAT & ADT. As outlined by Hussain *et al.*, data for low-volume must be interpreted under the light of a less mature nature and therefore should be interpreted with caution—while those might benefit from local treatment (10,14). It is of note that differentiation according to disease volume was based on conventional staging [computerized tomography (CT) or magnetic resonance imaging (MRI) and bone scanning] in ARASENS and PEACE-1. As a consequence, ongoing research is mandatory to answer the question whether current disease stratifications (CHAARTED, LATITUDE) are fully applicable for 'modern' staging relying on prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET-CT). Taking together, the stratified data of the ARASENS trial reported by Hussain *et al.* underline the role of triplet therapy in the setting of high-volume mHSPC. Greater uncertainty ongoingly exists for low-volume mHSPC patients due to the immature nature of the current data. Since some low-volume patients (e.g., young patients with aggressive tumor or patients with high-risk disease) could profit from triplet therapy, both triplet therapy as well as doublet therapy (ARAT & ADT) should be taken into account when treatment decisions are made.

Finally, the study by Hussain *et al.*—together with various landmark trials investigating treatment intensification in mHSPC patients in the past decade—should remind the uro-oncology community to deliver evidence-based care for mHSPC patients. As recently outlined by Chen *et al.*, real world data from around the world demonstrated an alarming dismal adoption of combination therapy for mHSPC patients clearly indicating a need for greater awareness and hence, uptake of treatment intensification for mHSPC patients (15). Within this context, it must be emphasized that above outlined considerations regarding treatment intensification might not be realizable in everyday practice in some parts of the world due to potential lack of financial reimbursement or availability in some parts of the world (16-18).

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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