1417P Mixed treatment comparisons evaluating contemporary therapies in metastatic castration sensitive prostate cancer (mCSPC): A living systematic review

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Background: Results from recent trials (PEACE-1, and ARASENS), the disease heterogeneity in mCSPC and lack of direct comparisons between triplets and novel hormonal therapy (NHT) doublets prompted us to assess the comparative effectiveness of contemporary treatments accounting for volume of disease.

Methods: This living review was conducted using the living interactive evidence (LIvE) synthesis framework. Phase II/III randomized controlled trials (RCTs) assessing first-line treatment options in mCSPC were included. Outcomes of interest included overall survival (OS), progression free survival (PFS), and grade 3 or higher adverse events (AEs). Fixed-effect frequentist network meta-analysis (NMA) was conducted to compute mixed treatment comparisons. P-scores were used to assess the relative treatment rankings.

Results: Of 28791 studies identified till date (25th April 2022), a total of 10 RCTs with 11043 patients and 9 unique treatment arms are included in this living review. In overall population, darolutamide triplet (DARO+D+ADT; rank 1; HR 0.68; 95% CI: 0.57-0.81), abiraterone acetate triplet (AAP+D+ADT; rank 2; HR 0.75; 95% CI: 0.59-0.95) significantly improved OS compared to docetaxel (D)+ADT (rank 6) but not compared to NHT doublets. In patients with high volume of disease, AAP+D+ADT (rank 1) significantly improved OS compared to D+ADT (rank 5; HR: 0.72; 95% CI: 0.55-0.95) but not compared to AAP+ADT (rank 2), enzalutamide (E)+ADT (rank 3), and apalutamide (APA)+ADT (rank 4). In low volume of disease, AAP+D+ADT (rank 4) did not significantly improve OS compared to APA+ADT (rank 1), AAP+ADT (rank 2), E+ADT (rank 3), and D+ADT (rank 5). The results were consistent excluding patients who received docetaxel in ENZAMET, ARCHES, and TITAN trials. The results were consistent for PFS outcome. DARO+D+ADT and AAP+D+ADT were ranked as the least safe options (rank 8, and 7, respectively) in terms of grade 3 or higher AEs.

Conclusions: The potential benefit with triplet therapy must be interpreted with caution accounting for volume of disease. Triplets may be favored in high volume whereas NHT doublets may be a preferred option in low volume of disease.

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1418P Extensive alteration of androgen precursor levels after castration in prostate cancer patients and their association with active androgen level: Importance for treatment intensification

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Background: The impact of castration on levels of steroid precursors of active androgens (testosterone or dihydrotestosterone (DHT)) is not well-characterized. We report the modulation by castration of gonadal and extragonadal androgen precursor steroids and their association with DHT and testosterone levels.

Methods: 116 serum samples were collected from 99 prostate cancer patients and categorized either as eugonadal, castration-sensitive (CSPC), castration-resistant (CRPC) or CRPC under abiraterone acetate. Serum levels of 15 steroids were measured using mass spectrometry and compared between groups using ANOVA. Intrapatient association of steroid levels and the androgens testosterone and DHT were assessed using Pearson correlation and linear regression.

Results: Testosterone, DHT, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androsterone, androstenediol, estrone, estrone-sulfate, estradiol, androsterone/3α-diol-3/3α-diol-17-glucuronide levels were statistically significantly decreased in CSPC compared to eugonadal (treatment-naïve) patients. Testosterone levels were strongly associated with multiple steroids under eugonadal conditions, whereas they were sparsely affected by precursor steroids in castrated patients. By contrast, DHT levels under androgen deprivation therapy (ADT) were associated with testosterone and the backdoor pathway metabolite androsterone. In CRPC patients, levels of androstenedione were significantly associated with testosterone level, while testosterone was the only steroid which predicted DHT levels.

Conclusions: ADT significantly reduces the levels of 13 circulating steroids. Upon ADT initiation, the backdoor pathway metabolite androsterone strongly predicted DHT levels. Under CRPC conditions, androstenedione was significantly associated with testosterone levels suggesting the presence of tumor-related circulating androgens in these patients. These results provide further rationale to intensify treatments with androgen receptor axis signalling pathway inhibitors in patients with prostate cancer.

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1419P Radiobiological parameters for the assessment of 177Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer

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Background: The lack of robust radiobiological data hampers the further optimization of emerging ^{177}Lu-PSMA-directed radioligand therapy (RLT). This study aims to explore several conventional radiobiological parameters in the assessment of outcomes in tumor and normal organs at risk (OARs) for castration-resistant prostate cancer (CRPC) patients.

Methods: 20 patients received a median of 3 (range 1−6, a totally of 86 cycles) ^{177}Lu-PSMA-617 RLT were retrospectively included. Hematological status, renal and liver function, and serum PSA test before and within two weeks post-therapy were documented. Pre-therapy PSMA-PET/CT image dates were collected to establish CT-based organ segmentation. The post-therapy dosimetry of each patient was measured using at least 3-time-points SPECT/CT imaging. PSA was used to determine therapy response, and the related adverse events were documented. Dose parameters including conventional radiobiological such as absorbed dose, integral dose (D10/50/90), biologically effective doses (BED) and cumulated BEDs (cBED) were tested.

Results: All patients are well-tolerated and 19/20 patients received a partial response post-therapy. The dosimetry evaluation demonstrated a high absorbed dose in tumors compared to OARs ($p<.0001$). The $Dose_{mean/max/sum}$ of target organs decreases as the treatment cycle increases. The absorbed dose in non-tumor-bearing bones is significantly correlated with hematological AEs (G2-4) ($p<.05$). The patients with larger PET-based tumor volumes present higher absorbed doses in tumor and OARs (also when normalized to the administered activity). The highest D10/50/90 was received by tumor-bearing bone, the whole-body tumor and lymph/visceral regions respectively compared to OARs. $BED_{1.5}$ (AUROC: 0.633) and $cBED_{1.5}$ (AUROC: 0.714) demonstrated aggregable diagnostic accuracy in detecting better post-treatment PSA outcomes.

Conclusions: Despite the limited number of patients in this study, the preliminary results encourage the exploration of radiobiological models in the assessment of PSMA-RLT. In-depth analysis and interpretation of these radiobiological parameters are still ongoing.

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