Is precision medicine possible in patients with mCRPC?

Optimal treatment sequencing in the area of triplet therapies for hormone-sensitive disease

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During the last decade, treatment of metastatic hormone sensitive prostate cancer (mHSPC) has evolved from Androgen deprivation therapy (ADT) alone to combined treatment concepts. Numerous prospective randomised controlled trails (RCT), testing ADT in combination with new hormonal agents (NHA) or Docetaxel chemotherapy upfront have demonstrated a substantial overall survival (OS) benefit vs. ADT alone, is meanwhile defined as standard of care for men suffering from mHSPC [1-6]. Given the various drugs approved for mHSPC treatment, consideration of patients´ disease extent (volume and risk categories) and comorbidity are crucial to select the optimal therapy.

Despite these significant advances, most patients, especially those with high volume/risk tumours, ultimately will progress to metastatic castration resistant prostate cancer (mCRPC). Due to the lack of data from prospective trials, several rules have been established to guide physicians to individually select the optimal treatment sequence: 1. expose to as many drugs as possible during mCRPC 2. find the optimal timing for therapy switch by using regular imaging, biomarker, pain and quality of life assessment 3. response to drug and drug class of previous therapy largely influences the choice of the next treatment line. E.g. due to various mechanisms of cross resistance, sequencing NHA such as Abiraterone followed by Enzalutamide or vice versa, has been shown to be inferior to PARP-Inhibitor treatment for men with homologous recombination repair (HRR) gene alterations or to second line chemotherapy with Cabacitaxel [7, 8]. 4. LU177-PSMA-Ligand therapy may offer some advantages over Cabacitaxel for some patients previously treated with NHA and Docetaxel [9].

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More recently, triple therapy combining ADT with Docetaxel plus NHA have been tested against ADT/Docetaxel in mHSPC patients. The multi-institutional investigator-initiated PEACE-1 trial concurrently added Abiraterone to ADT/Docetaxel and could establish an overall survival benefit in favour of the triple approach for all studied men (10). However, subgroup analysis revealed only a value for men with synchronous high volume mHSPC according to the CHAARTED criteria (HR 0.72, 95% CI 0.55–0.95) while the point estimate for the HR for was less pronounced for the subgroup of patients with low-volume mHSPC (HR 0.83, 95% CI 0.5–1.38).

The ARASENSE RCT again defined ADT/Docetaxel (plus placebo) as standard of care (SOC) and added Darolutamide in the experimental arm in mHSPC all-comer patients [11]. Darolutamide is so far approved only for men with nonmetastatic CRPC [12]. Again, the trial was in favour of the triple according to OS analysis and to all secondary endpoints. Subgroup analysis was positive for many predefined clinical categories, however, a stratification between high vs. low volume was not reported. In conclusion, both large prospectively randomised trials managed to establish a substantial benefit in favour of the triple vs. ADT/Docetaxel and the authors concluded that the triple approach may be considered the new SOC. Several limitations, however, deserve to be mentioned: 1. the exact patient population benefiting from the triple therapy needs to be defined. 2. the triple therapy has never been tested against ADT/NHA, which is currently considered SOC. In their summary from the 2021 APCCC meeting, the expert panel concluded that the triple therapy should focus on synchronous high volume mHSPC patients that are fit for chemotherapy. The lack of data with respect to the ADT/NHA comparison and the increased toxicity related to cytotoxic therapy need to be discussed with the patient [13].

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The concurrent application of three mHSPC drugs upfront raises the important question about the optimal sequence for progressing mCRPC. Little if anything is known about the efficacy of subsequent therapies. For the ARASENSE trial [11], 45.9% (n=299) of patients in the Darolutamide group and 19.1% (n=125) of patients in the placebo group were receiving ongoing study treatment. Subsequent life-prolonging systemic antineoplastic therapy is reported in the supplementary appendix. Accordingly, in the experimental arm, 56.8% vs. 75.6% in the control arm received life prolonging drugs beyond progression. Among these therapies, more than 50% received another NHA (predominantly Abiraterone) and roughly 40% were treated with another line of chemotherapy, with half of them getting re-exposed to Docetaxel. Unfortunately, the detailed response rates by drug class or progression free survival 2 (PFS2) as a surrogate for response to the next treatment line were not reported.

What can we learn from other trials? By simply looking at the inclusion criteria for current mCRPC drugs, most of the trials predominantly included men treated with ADT only for mHSPC, and only the latest trials e.g., the PROPEL trial, leading to the approval of Abiraterone in combination with Olaparip in an all-comer population accepted pre-treatment with an NHA (except of Abiraterone) or Docetaxel for mHSPC [14], but none of those patients received concurrent Docetaxel plus a NHA upfront. Recommendation of subsequent treatment strategies, therefore, need to be extrapolated from previous metastatic prostate cancer trials.

Sequencing NHA as first line mCRPC treatment after triple therapy

The concept of using Abiraterone within the triple therapy as suggested by the PEACE-1 consortium means that Abiraterone is continued beyond concurrent Docetaxel chemotherapy until progression [10]. Since Enzalutamide is the only approved hormonal drug beside Abiraterone in mCRPC, adding Enzalutamide would be "in label". However, data from sequencing studies revealed poor response rates due to several mechanisms of cross resistance between both drugs. Expected PFS rates range between 2-3 months and no survival benefit could be established [15]. Darolutamide as suggested in ARASENSE has not yet been tested in other mHSPC trials and is not approved for mCRPC. Therefore, limited data is reported with respect to sequential therapy.

The ARAMIS study evaluated the efficacy and safety of Darolutamide in nonmetastatic CRPC [12]. Among Darolutamide patients who entered active or long-term follow-up for survival (n=315), 112 (35.6%) patients subsequently received Abiraterone as a life-prolonging therapy. However, no efficacy or safety outcomes are available for these patients. While sequencing Enzalutamide after Darolutamide may not be considered due to the congruent mode of action, adding Abiraterone might nevertheless be an option.

Data from the TITAN study, where mHSPC patients were treated with ADT in combination with Apalutamide until progression, suggested, that the rate of AR mutations is limited under Apalutamide exposition (4). Accordingly, NHA treatment (predominantely Abirateron) provided a similar PFS2 compared to chemotherapy as first-line mCRPC treatment. Whether these data may be extrapolated to the use of Darolutamide in the context of triple therapy remains questioned.

Sequencing chemotherapy as first line mCRPC treatment after triple therapy

The concept of early Docetaxel chemotherapy for mHSPC has been established already in 2014 after reporting compelling data from the CHAARTED, GETUG-AFU15 and the STAMPEDE trials [1,2]. Subgroup analysis of GETUG suggested that Docetaxel re-exposition after early Docetaxel is inferior to sequencing with Abiraterone or Enzalutamide. Therefore, Cabacitaxel would be the preferred chemotherapy line beyond progression after early Docetaxel. Cabacitaxel is approved for mCRPC patients pre-treated with Docetaxel in mCRPC patients with a significant OS benefit compared to Mitoxantrone or a second line of NHA. However, the efficacy of Cabacitaxel has not yet been reported in the context of men progressing after triple therapy.

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Sequencing PARP-inhibitors as first line mCRPC treatment after triple therapy

Olaparib is the first PARP-I that is approved for mCRPC patients with a BRCA1/2 mutation progressing after Abiraterone and/or Enzalutamide [7]. Since two third of patients included in the pivotal PROFOUND trial were also exposed to sequential Docetaxel chemotherapy, Olaparib is considered as a second or third line mCRPC treatment. These data have been extrapolated to the current treatment landscape and prior NHA +/- chemotherapy may have been given also for mHSPC patients. Progression after triple therapy would therefore be "in label" for the prescription of Olaparib, when somatic or germline BRCA mutations are detected. However, again no data is available indicating the efficacy of Olaparib for patients pre-treated with triple therapy. More recently, Olaparib in combination with Abiraterone is approved for mCRPC all-comer populations regardless of their HRR status [14]. However, the very current label recommends the combinational treatment for "mCRPC patients in whom chemotherapy is not yet clinically indicated". This would exclude patients pre-treated with Abiraterone (with concurrent chemotherapy) or any other prior chemotherapy.

Sequencing LU177-PSMA-Ligand first line mCRPC treatment after triple therapy

For many years LU177-PSMA-Ligand therapy has been considered as an individual mCRPC treatment concept for intensively pre-treated patients with multiple PSMA positive lesions on PSMA-PET scan. Most recently, with positive results from the RC Vision trial, this concept is approved for mCRPC patients, pre-treated with at least one line of NHA and one line of chemotherapy [17]. With this label in mind, a patient progressing after any of the two triple concepts would already fulfil criteria for reimbursement and thus LU177-PSMA-Ligand could be considered as first line mCRPC therapy.

In conclusion, the optimal treatment sequence for men progressing after one of the triple therapy concepts needs to be defined. According the rationale derived from the discussed trials, Abiraterone (after Darolutamide), Olaparib in BRCA1 or 2 positive men, second line chemotherapy with Cabacitaxel and LU177-PSMA-Ligand therapy are valid mCRPC options. The optimal order, however, needs to be determined on upcoming prospective trials.

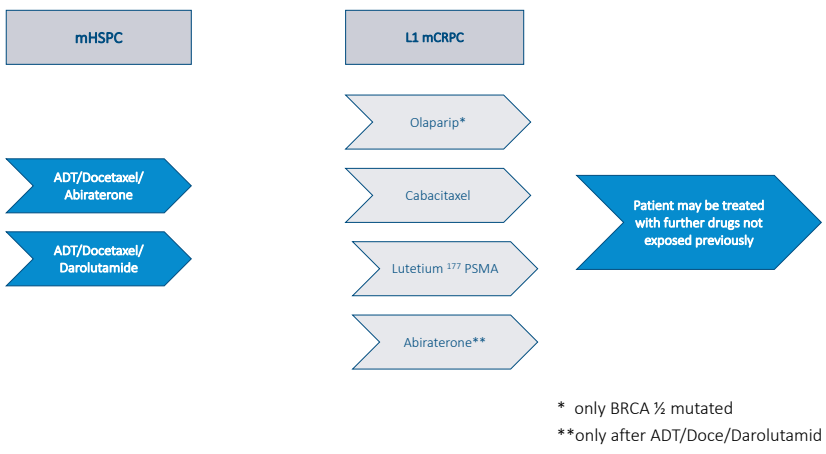

Figure 1. Plausible mCRPC sequences after triple therapy for mHSPC

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Sunday 12 March 18:00 - 18:10
Thematic Session: Is precision medicine possible in patients with mCRPC?
Yellow Area, eURO Auditorium 1