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Review Article

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Metastatic Hormone Sensitive Prostate Cancer, New Management Protocol, 2023

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Prelude:

Prostate cancer is the most common solid tumor in men. Although there have been many new developments in the last few years, metastatic castration resistant prostate cancer remains a deadly disease. This article provides an overview of currently approved treatment options as new and future treatment of prostate cancer.

Androgen deprivation therapy (ADT) alone has been the standard of care for many years in men with metastatic prostate cancer. Due to the limited survival under this monotherapy, many new treatment options have been developed in the last few years. Regarding hormone-sensitive prostate cancer, combination therapies of two or three agents of ADT, androgen receptor signaling inhibitors (ARSI) and chemotherapy (Multimodal treatment) have been established and led to a significant benefit in overall survival.

Patients with metastatic castration-resistant prostate cancer, there are many new therapeutic approaches. Chemotherapy alone has been the standard of care in this situation. In the last years, some new therapeutic options have been developed, which led to an improved survival after progression under chemotherapy. These therapies include ARSI, PARP inhibitors and Lu-PSMA radioligand therapy. The use of a bispecific T-cell engager (BiTE) in this setting is a new promising therapeutic approach, which has not been established as standard of care yet.

The latest advancements in systemic treatments were the addition of Poly ADP-Ribose Polymerase Inhibitor (PARPi) and radio-ligand therapies (RLT) to the armentarium. While check point inhibitors (CPI) have revolutionized anti-cancer treatment in many diseases they were less successful in prostate cancer.

The role of immunotherapy in prostate cancer is still under investigation. However, some activity has been noted for ipilimumab in men with mCRPC who were treated with at least one chemotherapy resulting progression of the disease.

Bispecific T Cell engager is a novel promising anti-cancer treatment modality in non-inflamed cancers, such as prostate cancer. These compounds re-direct T-cells to the tumor environment by targeting a cancer-specific epitope, such as PSMA in prostate cancer, which is linked to a component of the T-cell receptor (TCR). This mechanism recruits T-cells to the tumor milieu by binding to prostate cancer cells, which activates T-cells and enables immunologic anti-tumor response.

Keywords: mPCa, HSPC, ASRI, Lu-PSMA, CPI, BITE multimodal treatment.

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The treatment algorithm for metastatic prostate cancer has changed more in the last decade than in the previous 50 years. Testosterone suppression has for many years been the gold standard for men newly diagnosed with prostate cancer. However, randomised studies have now shown that escalation of therapy beyond.

In Metastatic Hormone Sensitive Prostate cancer (MHSPC), Testosterone deprivation results in profound and clinically meaningful survival benefits. This review aims to summarise the latest advancement in the field focusing on treatment of newly diagnosed hormone-sensitive prostate cancer.

Introduction:

With more than 1.4 million new cases in 2020 and an increasing incidence trend, prostate cancer maintains its position as the second most diagnosed cancer among men worldwide *Denovo* metastatic prostate cancer accounts for around 15% of all prostate cancer cases in western countries, but it is responsible for the majority of prostate cancer-related deaths and imposes a significant socio-economic burden when compared with locally recurrent prostate cancer.[1]

In the USA, the five-year overall survival (OS) for metastatic disease is only 32%, compared with almost 100% for localised or locally advanced disease.[3] Since the seminal work of Huggins *et al.* androgen deprivation treatment (ADT), achieved through surgical or chemical castration, represents the cornerstone of metastatic prostate cancer treatment.[4]

In the last decade, treatment intensification with the addition of new hormonal agents or chemotherapy to ADT was shown to extend progression-free survival (PFS) and OS in several randomised controlled trials. Significantly, these treatments, namely docetaxel chemotherapy, enzalutamide and abiraterone acetate in combination with prednisolone (AAP), had already been proved effective in prolonging OS for patients with metastatic castration-resistant prostate cancer.[5-10]

1990s and early 2000s[11-15]. The results of the trials lead to the most recent improvements in the treatment algorithm of metastatic hormone-sensitive prostate cancer (mHSPC). Local RT or radiotherapy to the prostate, previously only used in the metastatic setting as palliative treatment to control lower urinary tract symptoms such as bleeding, also proved beneficial in a subgroup of patients with a low burden of disease (Table I).

In the STAMPEDE trial, local radiotherapy increased the three-year OS rate from 73% to 81% in patients with low volume disease, categorised as fewer than four bone metastasis (Oligo metastatic disease or OMPC) and no visceral lesions.[16] The observed benefit has been linked to the eradication of the main tumour reservoir capable of seeding new metastasis and increased the interest around local treatments for oligometastatic disease.

In the LATITUDE trial, ADT + Placebo (n = 597 pts.) was compared to ADT + AAP (n = 602 pts.). Only patients with high-risk newly diagnosed metastatic disease, ISUP grade > 4, at least three bone lesions or measurable visceral metastases were included. The combination of ADT + AAP reported significant OS improvement (HR = 0.62, 95% CI 0.51–0.76; p < 0.001) when compared to ADT alone.

Table I : *Phase 3 Trials directly or indirectly involved in Triplet therapy for mHPC*

Study	Drugs	No. of Patients	Receiving Docetaxel	OS Outcome HR[95%CI].
Arches[5]	Enza+Doci	1150	18	0.74
Enzamet[7]	Enza+Doci	1125	15	0.82
Arasens[22]	Darotamide+Doci	1305	100	0.68
PEACE-1[23]	Abi+Doci+RT	1172	61	0.75

In the TITAN study, apalutamide + ADT (n = 525) was compared to ADT + Placebo (n = 527) in patients with mHSPC. The study reported superior OS in favor for the combination arm.

PEACE-1 is a complex study and consisted of four arms. At this point, only the combination therapy of ADT + docetaxel with or without abiraterone acetate and prednisone (AAP) were considered for analyses. The median rPFS was prolonged by 2.5 years in patients who received the AAP containing triplet (HR = 0.5, 95% CI 0.40–0.62; $p < 0.0001$). Furthermore, there was a 25% reduction in the risk of death in patients who received the triplet (HR = 0.75, 95% CI 0.59–0.95); $p = 0.017$).

Following the findings described above, a new generation of randomised controlled trials aimed to investigate the benefit of associating both chemotherapy and new hormonal agents for mHSPC (Table 1). In this review we aim to summarise the latest evidence derived from trials where patients with mHSPC were treated with triplet therapy (docetaxel plus new hormonal agent plus ADT) and describe the potential impact on current clinical practice (Table I).

The first data to explore the effect of androgen receptor targeted agents plus taxane 'triplet' approach were the combination of apalutamide or enzalutamide, two second-generation non-steroidal antiandrogens, with docetaxel in the TITAN, ARCHES and ENZAMET trials, respectively investigating apalutamide, enzalutamide, and enzalutamide in combination with ADT versus standard of care.[17]

The trials included subgroups of patients who also received up to six cycles of docetaxel in the hormone-sensitive setting, either before enrolment in the trial or, in the case of ENZAMET, after starting enzalutamide. However, it is worth noting that none of these trials were powered to compare those patients receiving the triplet versus the doublet therapy, and the cohort receiving triplet therapy was relatively small in each study. No dedicated randomised controlled trials have explored these specific drug combinations for patients with mHSPC.

The TITAN trial investigated the combination of apalutamide plus ADT versus placebo plus ADT, proving the superiority of the experimental arm in terms of OS (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.51–0.89). A small subgroup of 113 patients (10.7%), equally distributed between the two arms, received docetaxel prior to trial enrolment. Due to the low number of patients in this subgroup and the even lower number of events (only 20 patients had died at the time of data cut-off across the two arms), no conclusions can be drawn regarding the benefit of adding apalutamide in the subgroup pretreated with docetaxel (HR 1.27; 95% CI 0.52–3.09). No data are available for the docetaxel subgroup in the updated results presented at 48 months of follow-up.[18]

Similarly, the ARCHES trial compared enzalutamide plus ADT versus placebo plus ADT, and included a subgroup of 205 patients (17.8%) who received prior docetaxel, with 180/205 patients receiving the full six-cycle course. The trial met its primary endpoint, showing a 61% risk reduction for radiological progression in favour of the enzalutamide arm. The prespecified subgroup analysis confirmed the progression-free survival (PFS) benefit of enzalutamide in patients pretreated with docetaxel (HR 0.53; 95% CI 0.31–0.92). An update of the trial results was presented at ESMO 2021: OS benefit in the docetaxel (HR 0.74; 95% CI 0.46–1.20) subgroup was similar to the non-docetaxel subgroup.[19]

The ENZAMET trial randomised patients with mHSPC to enzalutamide plus ADT versus first generation non-steroidal antiandrogen plus ADT, with or without prior or concurrent docetaxel, achieving an increase in three-year OS from 72% to 80% for the enzalutamide arm (HR 0.67; 95% CI 0.52–0.86). Almost half of the patients enrolled received docetaxel either before (15.8%) or after (30.2%) enzalutamide was started. After a median follow-up of 34 months, patients also receiving docetaxel had a smaller, non-statistically significant benefit in OS from enzalutamide compared with the standard of care group (HR 0.90; 95% CI 0.62–1.31). However, a statistically significant benefit was observed for PFS (HR 0.48; 95% CI 0.37–0.62).[7] An update with an additional three years of follow-up was published in 2022. The benefit in OS for enzalutamide in this subgroup was more evident, although still non-statistically significant (HR 0.82; 95% CI 0.63–1.06).[20]

Darolutamide plus docetaxel for mHSPC

Darolutamide is a potent non-steroidal antiandrogen with the highest affinity for the androgen receptor among non-steroidal antiandrogens *in vitro*. Despite this suggestion of preclinical potency, there remain no head-to-head trials directly comparing the clinical effect of darolutamide with enzalutamide or apalutamide, although one key study showed reduced diffusion through the blood–brain barrier for darolutamide, leading to reduced incidence of central side-effects,[21] which remain a significant toxicity of enzalutamide.

The ARASENS trial randomised 1306 patients to darolutamide or placebo, both in combination with ADT and docetaxel. Of note, 86% of all enrolled patients had *de novo* mHSPC. At a median follow-up around 43 months, the addition of darolutamide was associated with a 32.5% reduction in the risk of death compared with placebo (HR 0.68; 95% CI 0.57–0.80). Darolutamide was also superior to placebo with respect to the secondary endpoints and the benefit was consistent across prespecified subgroups. Crucially, darolutamide did not increase the rate of G3 or higher adverse events, with most G3–4 adverse events in the study being detected during docetaxel treatment in both groups, such as neutropenia and febrile neutropenia. The incidence of G3–4 hypertension was double in the darolutamide group compared with placebo (6.4% versus 3.2%), although in line with previous trials involving new hormonal agents.[22]

Based on the results of the ARASENS trial, darolutamide has been approved by both FDA and NICE for the treatment of patients with mHSPC in combination with ADT and docetaxel.

Abiraterone acetate plus docetaxel for mHSPC

Abiraterone acetate is a prodrug of abiraterone, a selective CYP17 inhibitor, which is administered in combination with prednisolone. Together with ADT, AAP further depletes the level of circulating testosterone by blocking the synthesis by adrenal glands.

AAP was combined with ADT and docetaxel for mHSPC in the PEACE-1 trial, an open-label, randomised, phase 3 study with a 2×2 factorial design. The trial investigated the addition of AAP and/or local radiotherapy to standard of care, represented by ADT with or without docetaxel, as first-line treatment for *de novo* metastatic disease. Around 60% of patients in each arm received docetaxel as part of their treatment. The trial met its coprimary endpoints of radiological PFS and OS, reporting an 18% improvement in OS for the groups treated with AAP compared with standard of care (HR 0.82; 95% CI 0.69–0.98). The HR for OS was consistent for the subgroups treated with docetaxel (HR 0.75; 95% CI 0.59–0.95). Most patients managed to complete the six cycles of docetaxel regardless of the addition of AAP. In the ADT with docetaxel safety population, the incidence rate of G3 or higher adverse events was 63% in the AAP groups and 52% in the non-AAP groups. Similarly to ARASENS, the incidence of the most frequent adverse events was comparable between groups: most G3 adverse events occurred during docetaxel treatment with only hypertension (22% versus 13%) and aminotransferase increase (6% versus 1%) being significantly higher in the population treated with AAP.[23]

Critically, one can see that a key trial to evaluate androgen receptor targeted agents plus docetaxel versus androgen receptor targeted agents alone has not been done, and is unlikely to now be done.

A recent systematic review and meta-analysis, which selected 10 randomised controlled trials, including ARASENS and PEACE-1, confirmed that triplet therapy with darolutamide/AAP plus docetaxel and ADT improves OS compared with docetaxel and ADT alone. A key message seems to be that an androgen receptor targeted agent is the critical component in treatment intensification, and is likely to provide a greater benefit than docetaxel (Table II and III).

No benefit in OS was observed for triplet therapy versus doublet therapies with new hormonal agent plus ADT. The authors conclude that treatment intensification should be personalised, taking into account life expectancy and burden of disease.[24] Although not represented in granularity in any of the trials reviewed above, some clinicians use clinical features to guide decision making regarding therapy escalation. Features such as tumour de-differentiation, *ie* high Gleason score and presence of variant histology, or low prostate-specific antigen (PSA) to burden of disease have been used as indicators for chemotherapy rather than reliance on androgen receptor targeting alone.

Discussion and future directions:

The treatment paradigm for mHSPC is evolving with new chemo-androgen receptor targeted agents associations further prolonging OS in recent trials. The median survival for newly diagnosed patients with metastatic prostate cancer seen in the most up-to-date trials ARASENS and PEACE-1 is approaching five years having been 24 months in recent history with luteinising hormone-releasing hormone agonist therapy alone. It is clear the incremental steps in therapy escalation have had a very real impact in care, with a significant proportion of patients remaining disease free with a suppressed PSA three years into their treatment for metastatic disease. This represents a paradigm shift in care for men with prostate cancer.

While committees worldwide are working hard to update national and international guidelines, several ongoing randomised controlled trials are investigating new associations with the aim of advancing into the hormone-sensitive setting therapies that are available for mCRPC. These include 177Lu-PSMA-617, poly (ADP-ribose) polymerase (PARP) inhibitors, AKT inhibitors, and cyclin-dependent kinase (CDK) inhibitors, as well as more widely directed local therapies, either in unselected or selected populations (Table II).

Table II. *Phase 3 Trials directly or indirectly involved in Triplet therapy for mHPC*

STUDY	Clinical Trials gov. Identifier	Experimental drugs	Enrolment	Cohort selection	Expected Completion
AMPLITUDE	NCT04497844	Abi + niraparib	692	HRR Deficiency	Nov 2024
CAPtello281	NCT04493853	Abi+ Capivasertib	1000	PTEN Deficiency	Nov2025
Cyclone 3	NCTo5288166	Abi+abimaciclib	900	Unselected	October 2025
PRESTO	NCT03009981	SBRT+SOC	350	Oligometastic PC	June 2025
METRO	NCT04983095	SBRT+SOC	114	Oligometastic PC	Dec 2025
SPARKLE	NCT 05352178	SBRT+or Surgery+ SOC	873	Oligo Recurrent	April27
ARASAFE	NCT05676203	Darolutamide+ doci	250	Unselected	October 2025
PSMADDITION	NCT04720157	177Lu PSMA617	1126	Unselected	August 2024

Different options are already available for treatment intensification in the hormone-sensitive setting and we predict more will be available in the future. A key question remains as to whether it is possible to stratify patients based on clinical and biological factors to personalise options and optimise outcomes in clinical practice. Trials in progress such as PARADIGM (ClinicalTrials.gov identifier: NCT04067713) will hopefully help inform this unmet need.

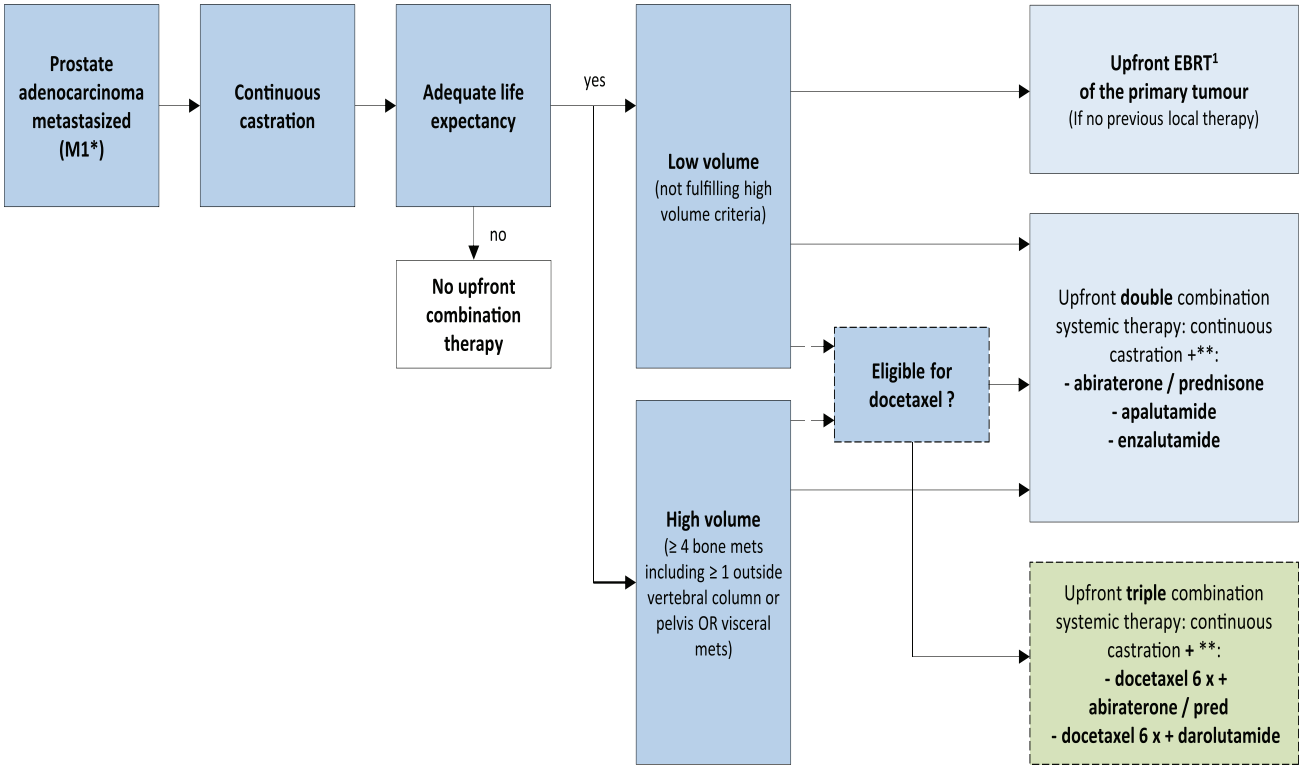

Table 3: EAU Guideline 2023 for metastasized (M1*) – disease, M+HSPC
(**h**ttps://uroweb.org/guidelines/prostate-cancer/chapter/citation-information)

Discussion of combination therapy with the patient and family including ADT plus systemic therapy with all M1 patients.All M1 Patients immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients(25).

At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction. Docetaxel may be offered only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease and who are fit for docetaxel (Table III).

Patients with Oligo metastatic status should be included in the trial and offered Standard systemic therapy with ADT combined with non-curative prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria/M1a disease. Additionally, the metastatic still remaining as active lesion may be offered SBRT (Stereotactic Body Radiation Therapy). Surgery in M1 Patients should be included in included in clinical trial only.[25]

Relugolix

Relugolix is the first oral androgen deprivation therapy approved by the FDA for advanced prostate cancer. It is a gonadotrophin-releasing hormone (GnRH) receptor antagonist that decreases gonadotropin release (ie, luteinizing hormone, follicle stimulating hormone), thereby decreasing the downstream production of testosterone by the testes in men.

Approval of relugolix was based on the HERO clinical trial (n = 622). In HERO, sustained testosterone suppression at 48 weeks was achieved in 96.7% of relugolix-treated patients compared with 88.8% with leuprolide. Risk of major adverse cardiovascular events was 54% lower with oral relugolix compared with leuprolide injections.[26]

Follow-up of M1 Patients

The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given. M1 patients, schedule follow-up at least every 3–6 months. A disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c and Serum PSA level measurements should be requested. In patients on long-term androgen deprivation therapy (ADT), measurement of initial bone mineral density to assess fracture risk. During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT. When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualized.[25]

Patients with ADT multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes.

Key points

- Treatment intensification with the addition of new hormonal agents or chemotherapy to ADT extend progression-free survival and overall survival
- The most recent improvements in the treatment algorithm of metastatic hormone-sensitive prostate cancer derived from a shift of treatment escalation to an earlier phase of the disease rather than to the introduction of completely new treatment options
- A systematic review and meta-analysis of 10 randomised controlled trials confirmed that triplet therapy with darolutamide/abiraterone acetate in combination with prednisolone plus docetaxel and androgen deprivation treatment improves overall survival compared with docetaxel and androgen deprivation treatment alone
- An androgen receptor targeted agent is the critical component in treatment intensification and is likely to provide a greater benefit than docetaxel
- Median survival for newly diagnosed patients with metastatic prostate cancer seen in the most up-to-date trials is approaching five years, compared with 24 months with luteinising hormone-releasing hormone agonist therapy alone
- A key question remains as to whether it is possible to stratify patients based on clinical and biological factors to personalise options and optimise outcomes in clinical practic

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