Review

De Novo Metastatic Prostate Cancer: Are We Moving towards a Personalized Treatment?

Claudia Piombino , Marco Oltrecolli , Elena Tonni , Marta Pirola , Rossana Matranga , Cinza Baldessari , Stefania Pipitone , Massimo Dominici , Roberto Sabbatini , Maria Giuseppa Vitale *

Posted Date: 11 September 2023

doi: 10.20944/preprints202309.0633.v1

Keywords: metastatic hormone-sensitive prostate cancer; new hormonal agents; transcriptomic profiling; DNA damage repair genes; tumor suppressor genes; androgen receptor; immunotherapy; CDK4/6 inhibitors; PARP inhibitors; AKT inhibitors.

Review

De Novo Metastatic Prostate Cancer: Are We Moving towards a Personalized Treatment?

Claudia Piombino [1], Marco Oltrecolli [1], Elena Tonni [1], Marta Pirola [1], Rossana Matranga [1], Cinza Baldessari [1], Stefania Pipitone [1], Massimo Dominici [1,2], Roberto Sabbatini [1] and Maria Giuseppa Vitale [1,*]

[1] Division of Oncology, Department of Oncology and Hematology, University Hospital of Modena, 41124 Modena, Italy; claudia.piombino@outlook.com (C.P.); oltrecolli.marco@gmail.com (M.O.); elenatonni.et@gmail.com (E.T.); marta.pirola04@gmail.com (M.P.); rossanamatranga94@gmail.com (R.M.); baldessari.cinzia@aou.mo.it (C.B.); pipitone.stefania@aou.mo.it (S.P.); massimo.dominici@unimore.it (M.D.); sabbrob@unimore.it (R.S.); vitale.mariagiuseppa@aou.mo.it (M.G.V.)

[2] Laboratory of Cellular Therapy, Division of Oncology, Department of Medical and Surgical Sciences for Children & Adults, University of Modena and Reggio Emilia, Modena, Italy.

* Correspondence: vitale.mariagiuseppa@aou.mo.it

Simple Summary: *De novo* metastatic hormone-sensitive prostate cancer has usually a dismal prognosis that has slightly improved in the last years thanks to the introduction of new hormonal agents and chemotherapy combined with androgen deprivation therapy from the first-line setting. The randomised clinical trials that have furnished the current therapeutic options stratified patients according to clinical criteria that not necessarily reflect the biological rationale of the chosen therapy. With the accumulation of data on genomic features and transcriptomic profiling, several ongoing clinical trials are investigating new therapeutic approaches and the efficacy of a biomarker-guided treatment with the aim to define a personalized treatment in *de novo* metastatic hormone-sensitive prostate cancer.

Abstract: *De novo* metastatic hormone-sensitive PC (mHSPC) accounts for 5-10% of all prostate cancer (PC) diagnoses but it is responsible for nearly 50% of PC-related deaths. Since 2015, the prognosis of mHSPC has slightly improved thanks to the introduction of new hormonal agents and chemotherapy combined with androgen deprivation therapy from the first-line setting. This review describes the current therapeutic opportunities in *de novo* mHSPC, focusing on potential molecular biomarkers identified in the main clinical trials that have changed the standard of care, the genomic features of *de novo* mHSPC, and the principal ongoing trials that are investigating new therapeutic approaches and the efficacy of a biomarker-guided treatment in this setting. The road towards a personalized treatment for *de novo* mHSPC is still long considering that the randomized clinical trials, which have furnished the basis of the current therapeutic options, stratified patients according to clinical criteria that not necessarily reflect the biological rationale of the chosen therapy. The role of transcriptomic profiling of mHSPC as predictive biomarker requires further validation, as well as it remains to ascertain how the genomic alterations detected in mHSPC, that are considered predictive in the castration-resistant disease, can be exploited in the mHSPC setting.

Keywords: metastatic hormone-sensitive prostate cancer; new hormonal agents; transcriptomic profiling; DNA damage repair genes; tumor suppressor genes; androgen receptor; immunotherapy; CDK4/6 inhibitors; PARP inhibitors; AKT inhibitors

1. Introduction

According to GLOBOCAN 2020, almost a million and half of new cases of prostate cancer (PC) and approximately 400.000 PC-related deaths were reported in 2020 globally [1]. *De novo* metastatic

 doi:10.20944/preprints202309.0633.v1

hormone-sensitive PC (mHSPC) accounts for 5-10% of all PC diagnoses but it is responsible for nearly 50% of PC related deaths [2,3]. The incidence of *de novo* mHSPC is rising in the Western countries, probably due to the introduction of new diagnostic tool in the imaging of PC, such as PSMA-PET, and a reduction in PSA opportunistic screening [4–6]. *De novo* mHSPC is characterized by an aggressive course with shorter time of onset of castration resistance and worse overall survival (OS) compared to metachronous mHSPC [7]. Since 2015, the prognosis of mHSPC has slightly improved thanks to the introduction of new hormonal agents (NHA) and chemotherapy combined with androgen deprivation therapy (ADT) from the first-line setting [8–14]. Nonetheless, the current therapeutic decision-making in mHSPC, unlike in metastatic castration-resistant PC (mCRPC), is still based on clinical features (e.g., high-volume vs. low-volume disease, visceral vs. bone-only metastasis) considering that clinical trials evaluating molecular biomarker-guided treatment of mHSPC are still ongoing.

The aim of this review was to describe the current therapeutic opportunities in *de novo* mHSPC, focusing on potential molecular biomarkers identified in the main clinical trials that have changed the standard of care (SOC), the genomic features of *de novo* mHSPC, and the principal ongoing trials that are investigating new therapeutic approaches and the efficacy of a biomarker-guided treatment in this setting.

2. Current therapeutic opportunities in *de novo* mHSPC

2.1. Doublet therapy

2.1.1. Docetaxel plus ADT

The first study that redefined the treatment paradigm in mHSPC has been the CHAARTED (ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial [8]. This randomized phase III trial study enrolled 790 men affected by mHSPC (575 of them with *de novo* disease) with the aim to verify the superiority of upfront docetaxel 75 mg/mq given every 3 weeks for six cycles in association with ADT over ADT alone. After a median follow-up of 53.7 months, an absolute benefit in terms of mOS of 16.8 months was observed in the combination treatment arm compared to ADT alone (mOS: 51.2 vs. 34.4 months; HR: 0.63; 95%CI: 0.50-0.79; $p<0.001$) in patients with high-volume disease (defined by at least 4 bone metastatic lesions with at least one beyond the vertebral bodies and pelvis and/or by the presence of visceral metastases), while no benefit was observed in patients with low-volume disease [15]. A transcriptional profiling of primary PC samples obtained from 160 patients enrolled in this trial (of which 88% with *de novo* mHSPC and 78% with high-volume disease) was performed by Hamid and colleagues [16] using the PAM50 classifier (luminal A, luminal B and basal subgroups), the Decipher genomic classifier, and androgen receptor activity (AR-A, classified as average vs. lower) [17–19]. The analysis revealed a predominance of luminal B (50%) and basal (48%) subtypes, lower AR-A and high Decipher risk disease. Luminal B subtype benefited significantly from the addiction of docetaxel to ADT in terms of OS, in contrast to basal subtype which showed no OS benefit even in case of high-volume disease. In multivariate analysis, higher Decipher risk and lower AR-A significantly associated with poorer OS. Additionally, the combination therapy conferred greater improvements in OS in presence of higher Decipher risk. This study proposed both prognostic and predictive roles for transcriptional subtyping in mHSPC.

2.1.2. Abiraterone plus ADT

The double-blind phase III trial LATITUDE [10] was the first study to demonstrate the benefit of an upfront combination therapy with an NHA. A total of 1199 patients affected by *de novo* high-risk mHSPC, defined by at least two of the three risk factors (Gleason score ≥ 8, at least three bone lesions, and the presence of visceral metastasis), were 1:1 randomised to receive abiraterone acetate plus prednisone (or prednisolone) plus ADT versus placebo plus ADT. Considering the notable benefit in terms of radiological progression free survival (rPFS) and OS observed in the experimental

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 September 2023 doi:10.20944/preprints202309.0633.v1

group at an interim analysis, the trial was subsequently unblinded and crossover was allowed. At the time of final OS analysis (median follow-up 51.8 months), 72 patients had crossed over to abiraterone acetate from the placebo group; the mOS was 53.3 months (95%CI: 48.2 months to not reached (NR)) in the experimental arm vs. 36.5 months (95%CI: 33.5-40.0 months) in the ADT alone arm (HR: 0.66, p<0.0001) [20]. No analysis on predictive biomarkers of response to abiraterone acetate was reported. An interesting multivariable model using data from the LATITUDE trial identified 11 prognostic variables commonly assessed in clinical practice (performance status, number of skeletal metastases, Gleason score, presence of liver metastasis, worst pain score, albumin, LDH level, PSA level, haemoglobin level, and treatment regimen) that accurately predict prognosis and improve risk stratification in *de novo* mHSPC [21].

2.1.3. Enzalutamide plus ADT

The role of the NHA enzalutamide associated with ADT as upfront therapy in mHSPC has been investigated in two phase III clinical trials. In the double-blind ARCHES trial [13], a total of 1150 patients with mHSPC were 1:1 randomly assigned to receive enzalutamide plus ADT or placebo plus ADT. Previous treatment with docetaxel was allowed. Enzalutamide significantly reduced the risk of radiographic disease progression or death compared with ADT alone by 61% (HR: 0.39; 95%CI: 0.30-0.50; p<0.001) irrespectively of prior local and systemic treatment, disease volume, and risk [22]. A *post hoc* analysis demonstrated the clinical benefit of enzalutamide in both cases of *de novo* mHSPC and metachronous mHSPC [23]. After unblinding, 180 progression-free patients randomly assigned to placebo plus ADT crossed over to enzalutamide plus ADT. The final prespecified analysis of OS (median follow-up 44.6 months) showed that enzalutamide reduced risk of death by 34% versus ADT alone (median NR in either group; HR: 0.66; 95%CI: 0.53-0.81; p<0.001) [24].

In the ENZAMET study [12], a total of 1125 patients affected by mHSPC were 1:1 randomly assigned to receive enzalutamide or a non-nonsteroidal first-generation antiandrogen (bicalutamide, flutamide, or nilutamide) in association with ADT. The 52% of the patients had high-volume disease. Prior course of six cycles of docetaxel was given to 65% of patients in the enzalutamide group and to 76% of patients in the control group. Besides, concurrent upfront docetaxel was permitted after a protocol amendment early in accrual. At the planned primary OS analysis (median follow-up 68 months), the mOS was NR in both groups (HR: 0.70; 95%CI: 0.58-0.84; p<0.0001), with 5-year OS of 57% in the control group and 67% in the enzalutamide group. Enzalutamide benefit in terms of OS was consistent across predefined prognostic subgroups (*de novo* vs. metachronous mHSPC, high-volume vs. low-volume disease) and in those who received concurrent docetaxel [25]. Unfortunately, no analysis on predictive biomarkers of response to enzalutamide was described.

2.1.3. Apalutamide plus ADT

The efficacy of the NHA apalutamide plus ADT compared to ADT plus placebo was evaluated in the double-blind phase III trial TITAN [14]. Eligible patients were required to have mHSPC with at least one lesion detectable on bone scanning; previous docetaxel therapy was allowed. Among 1052 enrolled patients, 10.7% had received previous docetaxel therapy and 62.7% had high-volume disease; more than 80% of patients had *de novo* disease. The 40% of the patients in the placebo group crossed over to apalutamide after the initial unblinding at 22.7 months of follow-up. At a median follow-up of 44 months, apalutamide plus ADT significantly reduced the risk of death by 35% compared to ADT alone (mOS: NR vs. 52.2 months; HR: 0.65; 95%CI: 0.53-0.79; p<0.0001) and by 48% after adjustment for crossover. Subgroup analysis suggested benefit for apalutamide in almost all subgroups including both low and high-volume disease; a trend towards favouring placebo in patients who had received prior docetaxel was registered, although these patients represented only 10% of the trial population and a post-hoc interaction test showed not interaction between the efficacy of apalutamide and prior docetaxel [26]. In a post hoc analysis, similarly to what performed by Hamid *et al.* [16], a transcriptional profiling of primary PC samples from 222 patients enrolled in TITAN revealed that most patients had a high Decipher risk disease. In the placebo group, patients with high Decipher risk had poorer prognosis than those with Decipher risk low to average, while no prognostic

 doi:10.20944/preprints202309.0633.v1

difference among these two different classes of risk was observed in the apalutamide group. Both basal and AR-A low subtypes showed significant benefit from apalutamide, suggesting that apalutamide is beneficial especially for the highest risk molecular subtypes [27]. A more sustained benefit with the addition of apalutamide to ADT in patients with a high Decipher genomic classifier score compared with patients with a low genomic classifier score was also confirmed in a cohort of 233 patients from the SPARTAN trial [28]. In an exploratory analysis investigating relationships between biomarkers and OS in TITAN, the presence of circulating tumoral DNA (ctDNA) or any androgen receptor (AR) genomic aberrations at baseline and any AR genomic aberrations or PI3K pathway activation at end of study treatment were significantly associated with poor OS in multivariate analyses from both treatment groups [29].

2.2. Triplet therapy

More recently, the efficacy of further treatment intensification with triplet therapy, consisting in the association of ADT with both docetaxel and NHA, has been investigated by the phase III trials ARASENS and PEACE-1. ARASENS [30] enrolled 1306 patients affected by mHSPC eligible for ADT and chemotherapy with docetaxel to receive either darolutamide or placebo in addition to docetaxel for six cycles and ADT. Most patients (86.1%) had *de novo* mHSPC. The primary analysis showed a 32.5% (HR: 0.68; 95%CI: 0.57-0.80; p<0.001) lower risk of death in the darolutamide group than in the placebo one: with a median follow-up of 43.7 months in the darolutamide arm and 42.4 months in the placebo arm, mOS resulted NR in the experimental group vs. 48.9 month in the control group. According to safety analyses, adverse events (AEs) of any grade were similar in both groups: the most common grade 3 or 4 AE was neutropenia associated with docetaxel. Post hoc analyses showed significant OS benefit in favour of the addition of darolutamide in all patients, with more consistent outcomes in high-volume (mOS: NR vs. 42.4 months; HR: 0.69; 95%CI: 0.57-0.82), high-risk (mOS: NR vs. 43.2 months; HR: 0.71; 95%CI: 0.58-0.86) and low-risk (mOS: NR vs. NR; HR: 0.62; 95%CI: 0.42-0.90) disease subgroups [31]. However, most of the patients included in the ARASENS trial had high-volume (77%) and/or high-risk (70%) disease: low-volume population was not well represented (only 23%). Thus, it is not possible to draw definitive conclusions for patients with low-volume disease.

PEACE-1 [32] was a 2 × 2 factorial design trial which enrolled 1173 patients with *de novo* mHSPC. Eligible participants were therefore randomly assigned in a 1:1:1:1 to receive the SOC (ADT alone or with docetaxel for six cycles; the 2017 amendment made the association of both mandatory), SOC plus external beam radiotherapy (EBRT) to the primary tumour, SOC plus abiraterone in association with prednisone, or SOC plus abiraterone and EBRT to the primary tumour. In order to assess the efficacy of abiraterone in addition to SOC, on the basis of the assumption of the absence of significant interactions between abiraterone and EBRT to the primary tumour, they conducted a 2X2 factorial analysis. They pooled the groups 2 by 2, distinguishing those who received abiraterone with or without EBRT to the primary tumour into one and comparing them to those who did not receive it (SOC with or without EBRT to the primary tumour). At a median follow-up of 3.5 years, the addition of abiraterone significantly improved median rPFS (4.46 vs. 2.22 years; HR: 0.54; 95%CI: 0.41-0.71) with a reduction of the relative risk of radiographic progression by 46%. With a median follow-up of 4.4 years, also a significant benefit in terms of mOS was reported in patients receiving abiraterone (5.72 vs. 4.72 years; HR: 0.82; 95%CI: 0.69-0.98; p=0.03), with a risk of death from any cause 18% lower than in those who didn't receive it. The effect of abiraterone was particularly marked in patients with high-volume disease (median rPFS: 4.46 vs. 2.03 years, HR: 0.50; mOS: NR vs. 4.43 years, HR: 0.75). From the safety point of view, abiraterone did not determine a significant increase in neutropenia, febrile neutropenia, fatigue, or neuropathy rates compared with ADT plus docetaxel alone; the only exceptions were hypertension, hypokalaemia, and higher levels of aminotransferases, which were more frequently reported in the group treated with abiraterone.

Both ARASENS and PEACE-1 showed that upfront treatment intensification with the combination of ADT, docetaxel, and NHA in *de novo* mHSPC could become a new SOC since it improved survival outcomes with an acceptable safety profile, especially in patients with high-volume disease. Up to now, no predictive biomarker of response to triplet therapy has been reported.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 September 2023 doi:10.20944/preprints202309.0633.v1

2.3. Oligometastatic prostate cancer

Oligometastatic PC (omPC) encompasses a heterogeneous group of tumours characterized by a low metastatic burden [33]. While some works define omPC on the basis of the number of metastases, ranging from 3 to 5 lesions, other authors adopt the criteria of low-volume disease according to CHAARTED trial [8] or low-risk disease according to LATITUDE trial [10] for the definition of omPC either *de novo* or recurrent [34]. Considering that *de novo* omPC has generally an indolent behaviour, with lymph node metastases only or minimal bone involvement, and it is associated with a better prognosis compared to patients with more than 5 lesions [35], a benefit from different treatment options may be observed. In fact, post hoc analysis of CHAARTED [8] and GETUG-AFU15 trials [36] showed that patients with low-volume disease had a much longer OS, without evidence that docetaxel improved OS, irrespective of whether patients received ADT plus docetaxel for *de novo* mHSPC or after prior local treatment [37]. By the other hand, in a post hoc analysis of the STAMPEDE trial arm G [11], the addition of abiraterone to ADT improved OS also in low-volume *de novo* mHSPC (HR: 0.60, 95%CI: 0.39-0.92) [38]. Similarly, upfront enzalutamide or apalutamide conferred a disease burden-independent advantage over ADT alone in the phase III pivotal studies [12–14].

Different therapeutic approaches in *de novo* omPC include locoregional treatments, mainly radiation therapy. In the HORRAD trial [39] 432 patients with primary bone mHSPC were randomised to receive ADT alone or ADT plus EBRT to the primary tumour; the subgroup analysis demonstrated a trend towards an OS benefit only in patients with less than 5 bone lesions (HR: 0.68, 95%CI: 0.42-1.10). These promising results were further investigated in the STAMPEDE trial arm H [40]: EBRT to the primary tumour significantly improved OS in patients with low metastatic burden according to CHAARTED criteria (HR: 0.68, 95%CI: 0.52-0.90; p = 0.007), reporting an increase of the 3-year survival rate from 73% to 81% with EBRT. In a recent phase II trial including 200 patients with *de novo* omPC (defined as 5 or fewer bone or extrapelvic lymph node metastases and no visceral metastases) randomised to receive either ADT or ADT plus radical local treatment of the primary tumour, both rPFS and OS were significantly improved in the arm with radical local treatment of the primary tumour [41]. However, opposite results have been recently presented at the last ASCO genitourinary symposium from the PEACE-1 trial [30]: in men with *de novo* low-volume mHSPC (at most 3 bone metastases with or without nodal involvement) combining prostate EBRT to systemic treatment did not improve OS [42]. The differences emerged in these trials are probably due to the different definition of low-volume diseases as well as the different systemic treatments administered to the patients. Nevertheless, EBRT to the primary tumour combined with the systemic treatment is recommended for patients with low-volume mHSPC according to ESMO and NCCN guidelines [43,44].

In addition to EBRT to the primary tumour, metastasis-directed therapy (MDT) is a debating issue. MDT is generally used to treat bone metastases or pathological lymph nodes. The only two prospective trials of stereotactic ablative radiotherapy (SABRT) versus observation, STOMP and ORIOLE, were focused only on metachronous omPC, demonstrating that MDT prolongs androgen deprivation-free survival and PFS compared to observation [45,46]. Although in *de novo* omPC there is no randomised trial evidence suggesting a benefit from MDT of all documented lesions, there is a strong consensus for a combined approach (ADT plus additional systemic therapy, local radiotherapy, and MDT) [43]. Available evidence derives from several case series in which a combined approach was investigated with encouraging results [48–51]. Many trials are ongoing to define whether the combination of ADT plus SABRT in *de novo* omPC improves outcomes compared with systemic treatment alone (NCT03298087, NCT05707468, NCT04983095, NCT04115007, NCT05223803, NCT04619069, NCT03784755, NCT05212857, NCT05209243).

The addition of radiation therapy to systemic treatment has a potential biological rationale: radiotherapy induces cell death, and the dying cells release “danger signals” that in turn might make cancer cells outside the radiation field more susceptible to an immune-mediated cytotoxic environment (the so-called abscopal effect) [52]. Moreover, radiation therapy might prevent metastasis-to-metastasis spread. Characterizing multiple metastases arising from PC in ten patients under ADT with whole-genome sequencing, Goundem et al. [53] demonstrated the existence of

 doi:10.20944/preprints202309.0633.v1

metastasis-to-metastasis spread, either through *de novo* monoclonal seeding of daughter metastases or through the transfer of multiple tumour clones between metastatic sites.

Although MDT appears to be effective in omPC, little is known about predictive biomarkers of response to the different treatment options available in this setting [54,55]. The study of predictive biomarkers might be useful to identify which patients could benefit from ADT only or ADT combined with chemotherapy, NHA and/or local treatments. The only data available derive from a pooled analysis of STOMP and ORIOLE trials, where the largest benefit of MDT in metachronous omPC was observed in patients with high-risk mutations defined as pathogenic somatic mutations within *ATM*, *BRCA1/2*, *Rb1*, or *TP53*, suggesting that a high-risk mutational signature may stratify treatment response after MDT [56].

3. Genomic features of mHSPC

The aim of therapy modulation and personalization in *de novo* mHSPC may be reached by the study of biology and biomarkers. However, the mutation profile of mHSPC is poorly characterized since sequencing efforts have focused on either localised PC or mCRPC. Progression from localized PC to mCRPC is characterised by accumulation of deleterious genomic alterations in the latter disease state. In detail, the most frequent altered genes in mCRPC are tumour suppressor genes (*RB1*, *TP53* and *PTEN*) and genes involved in androgen receptor (AR) pathway, chromatin remodelling (*KMT2C* and *KMT2D*), PI3K signalling (*AKT1* and *PIK3CA*), and DNA damage repair (DDR) (*BRCA2*, *BRCA1*, *ATM*, and *FANCA*) [57–59]. Different data seems to indicate that the mutation profile of mHSPC lies between localised PC and mCRPC, suggesting that the enrichment of deleterious alterations over time confers survival advantage to cancer cells inducing treatment resistance [60,61]. A systematic metanalysis [54] including 1682 mHSPC patients of whom 1248 (74%) with *de novo* disease from 11 studies pointed out that the most commonly altered genes, due to mutations or copy number alterations, were *TP53* (32%) and *PTEN* (20%), followed by genes involved in DDR (18%) with *BRCA2* as the most frequently mutated gene (7%); alterations in cell cycle signalling were reported in 7-13% of the cases. Tumours from patients with *de novo* mHSPC were enriched for mutations in *TP53* and *CDK12* compared with metachronous mHSPC, while cell cycle signalling, Wnt pathway, *PTEN* and *SPOP* alterations were more frequent in metachronous mHSPC. In high-volume disease according to CHAARTED criteria [8], *TP53*, *BRCA2*, *PIK3CA*, *RB1*, and *APC* were more frequently altered compared to low-volume disease. However, DNA source and definitions for genes alterations differed significantly among studies, including somatic alteration from formalin-fixed paraffin-embedded (FFPE) material as well as ctDNA. Among the studies included in the aforementioned metanalysis, a noteworthy observation derives from the targeted next-generation sequencing (tNGS) performed on 185 tumour samples obtained almost entirely from *de novo* mHSPC patients enrolled in the STAMPEDE trial: PI3K pathway aberration was observed in 43% of the cases, due to *PTEN* copy-number loss (34%) and/or inactivating mutations in *PIK3* or *AKT* (18%) [62].

3.1. The role of liquid biopsy

Most patients with *de novo* mHSPC will not undergo primary surgery; the histologic diagnosis is typically performed on prostatic biopsy. Therefore, liquid biopsy could add clinically relevant information in this setting. In a single-centre prospective cohort, Vanderkerhove et al. [63] detected a median plasma ctDNA fraction of 11% (range 2.0-84%) among 26 out of 35 (74%) untreated patients with *de novo* mHSPC; for the remaining 9 patients, ctDNA was not detectable. Higher ctDNA levels were identified in presence of visceral metastasis. The somatic analysis from ctDNA and tumour tissue revealed a mutational landscape similar to mCRPC, although without *AR* gene alterations: *TP53* and DDR genes mutations were identified in 47% and 21% of the cases, respectively. The rate of concordance for mutation detection between tumour tissue and ctDNA was 80%, suggesting that *de novo* mHSPC is a highly clonal disease at the diagnosis. By the other hand, in a cohort of 82 Chinese patients with *de novo* mHSPC, only 50% of patients had a ctDNA fraction >2% and the percentage of ctDNA positive patients was even lower (37%) in a cohort of 73 untreated mHSPC including both *de novo* and metachronous disease [64,65]. There are still challenges to overcome prior to introduce

 doi:10.20944/preprints202309.0633.v1

liquid biopsies in routine clinical practice, such as preanalytical aspects and low-circulating tumour content, considering that common PC copy number alterations such as *PTEN* or *CDH1* deletions are undetectable in presence of low ctDNA fraction [66]. Consequently, in patients with a low ctDNA fraction, tissue biopsy profiling remains more informative.

3.2. Prognostic information

From a prognostic point of view, data regarding the association between genetic alterations, time to castration resistance and OS in *de novo* mHSPC are partial, because they have been obtained from cohorts including both synchronous and metachronous metastatic disease. Among 424 cases of mHSPC including 275 patients with *de novo* disease, Stopsack et al. [67] reported a rate of progression to castration resistance 1.6 to 5-fold higher in presence of alterations in *AR*, *TP53*, cell cycle, and MYC pathways and approximately 1.5-fold lower with *SPOP* and Wnt pathway alterations; similarly, OS rate was 2 to 4-fold higher in presence of *AR* or cell cycle alterations, and 2 to 3-fold lower if *SPOP* or Wnt pathway was altered. Sequencing of FFPE tissue from biopsies of 43 patients affected by mHSPC of whom 30 with *de novo* disease revealed an incrementally poorer OS with cumulative mutations or alterations in the tumour suppressor genes *TP53*, *PTEN*, and *RB1* [61]; the negative prognostic value of alterations in *TP53*, *PTEN*, and *RB1* has been observed also in a cohort of 97 patients with mHSPC treated with first-line ADT plus docetaxel or abiraterone acetate, outperforming clinical criteria to predict early disease progression [68]. An association between shorter OS and alteration in *TP53*, *ATM* and DDR genes detected on plasma ctDNA was observed also among 53 patients with *de novo* or metachronous untreated mHSPC [65]. Finally, tNGS across 113 genes performed on 202 primary tumours samples obtained from patients with synchronous or metachronous mHSPC revealed a significantly shorter OS in presence of mutations or deep deletions of *RB1* [69].

The association between *SPOP* mutations and better prognosis has been also detected in a cohort of 121 men with *de novo* mHSPC treated with ADT: both median PFS and OS were significantly improved in the subset of 25 patients with *SPOP* mutated cancers (mPFS: 35 vs. 13 months, $p = 0.016$; mOS: 97 vs. 69 months, $p = 0.027$) [70]. SPOP protein is involved in ubiquitination and consequent proteasomal degradation of target proteins; in PC, SPOP seems to act as a tumour suppressor by targeting several proteins, including AR, SRC3 and BRD4 [71]. The hypothesis that *SPOP* mutated PC are primarily driven by AR signalling has been tested in a real-world setting: in a cohort of patients with *de novo* mHSPC undergoing ADT plus NHA, the presence of *SPOP* mutation compared with wild-type was associated with longer time to castration resistance and OS, while *SPOP* mutational status was not associated with time to castration resistance nor OS in a cohort treated with ADT plus docetaxel [72]. *SPOP* mutation may therefore be used as a predictive biomarker to guide treatment choice for patients with *de novo* mHSPC.

4. Ongoing phase III clinical trials testing new therapeutic approaches in mHSPC

Apart from trials focusing on NHA, ADT and chemotherapy with different schedules in mHSPC (ARANOTE NCT04736199, ARASAFE NCT05676203, LIBERTAS NCT05884398, NCT05956639), several other ongoing phase III clinical trials are investigating the role of new therapeutic approaches (immunotherapy, radiopharmaceuticals, and molecular target agents) in this setting (Table 1, Figure 1).

Table 1. Ongoing Phase 3 clinical trials testing new therapeutic approaches in mHSPC.

Official Title NCT Number	Control arm	Experimental arm(s)	Primary Endpoints	Status	Enrolment	Study start/completion date
KEYNOTE-991 NCT04191096	Placebo + Enzalutamide + ADT	Pembrolizumab + Enzalutamide + ADT	OS, rPFS	Active, not recruiting	1251 (actual)	2021-05-25/ 2026-02-02
PROSTRATEGY NCT03879122	ARM 1: ADT + Docetaxel for 6 cycles	ARM 2: ADT + Docetaxel for 6 cycle and then Nivolumab 3 mg/kg every 2 weeks for 12 months ARM 3: ADT + 2 cycles of Ipilimumab 3 mg/kg every 3 weeks, followed by 3 cycles of Docetaxel, 2 cycles of Ipilimumab, 3 cycles of Docetaxel, Nivolumab 3 mg/kg every 2 weeks for 12 months	OS	Active, not recruiting	135 (estimated)	2019-02-11/ 2024-12-31
PSMAddition NCT04720157	NHA + ADT	7.4 GBq (+/- 10%) 177Lu-PSMA-617, once every 6 weeks (+/- 1 week) for 6 cycles + NHA + ADT	rPFS	Recruiting	1126 (estimated)	2021-06-09/ 2026-02-11
CYCLONE-03 NCT05288166	Placebo + Abiraterone + Prednisone/Prednisolone	Abemaciclib + Abiraterone + Prednisone/Prednisolone	rPFS	Recruiting	900 (estimated)	2022-04-14/ 2027-10-01
TALAPRO-3 NCT04821622	Placebo + Enzalutamide	Talazoparib + Enzalutamide	rPFS	Active, not recruiting	599 (actual)	2021-05-12/ 2027-04-10
AMPLITUDE NCT04497844	Placebo + Abiraterone + Prednisone/Prednisolone	Niraparib + Abiraterone + Prednisone/Prednisolone	rPFS	Recruiting	692 (estimated)	2020-09-23/ 2027-05-27
CAPItello-281 NCT04493853	Placebo + Abiraterone + Prednisone/Prednisolone	Capivasertib + Abiraterone + Prednisone/Prednisolone	rPFS	Recruiting	1000 (estimated)	2020-07-13/ 2026-03-10

OS: Overall Survival; rPFS: radiographic progression-free survival; ADT: androgen deprivation therapy; GBq: Giga Becquerel; NHA: new hormonal agent.

doi:10.20944/preprints202309.0633.v1

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 11 September 2023 doi:10.20944/preprints202309.0633.v1

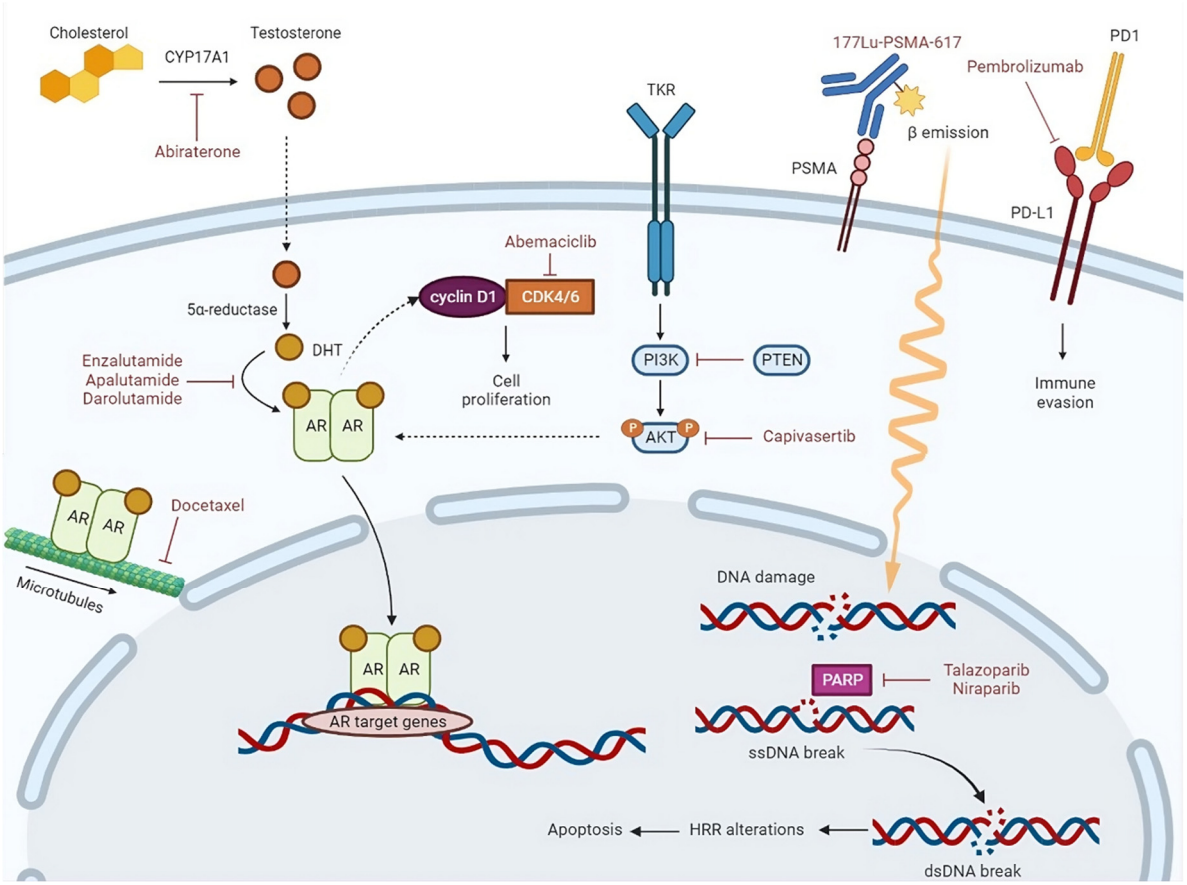

Figure 1. Abiraterone is an inhibitor of CYP17A1, a key enzyme in the steroidogenic pathway that produces testosterone. Testosterone is metabolized to dihydrotestosterone (DHT) by the enzyme 5α-reductase. The androgen receptor (AR), activated by binding of DHT in the cytoplasm, translocates into the nucleus where it acts as a DNA-binding transcription factor that regulates AR target genes expression. Enzalutamide, apalutamide and darolutamide competitively inhibit DHT binding to the AR, nuclear translocation of the AR, and DNA binding. Docetaxel inhibits AR nuclear translocation by targeting AR association with microtubules. During G1-S checkpoint, AR can bind to and activate cyclin D1 that by association with the cyclin-dependent kinases 4 and 6 (CDK4/6) contributes to cancer cell proliferation. Abemaciclib, a CDK4/6 inhibitor, induces cell cycle arrest and tumor growth inhibition. PI3K/AKT pathway is activated by binding of the ligands such as growth factors to tyrosine kinase receptor (TKR). AKT via phosphorylation regulates activation or suppression of several proteins involved in cell growth and proliferation. PTEN is the main downregulation protein of this pathway. AKT regulates transcriptional activity of the AR. Capivasertib, an AKT inhibitor, reduces AKT substrate phosphorylation and cell proliferation. The binding of the radioligand Lutetium-177(177Lu)-PSMA-617 to the prostate-specific membrane antigen (PSMA) results in its internalization and delivery of β-radiation into the cancer cells; radiations activate apoptosis by single-strand (ssDNA) and double-strand DNA (dsDNA) breaks. When a ssDNA break occurs, PARP recruitment and activation leads to DNA repair. In the presence of a PARP inhibitor, such as Talazoparib or Niraparib, unrepaired ssDNA breaks lead to dsDNA breaks by collapse of the stalled replication fork during DNA replication. In cells with homologous recombination repair (HRR) alterations, dsDNA breaks are repaired by the more error-prone non-homologous end-joining pathway, therefore causing genomic instability followed by apoptosis.

4.1. Immunotherapy

Although the expression of programmed death ligands 1 and 2 (PD-L1 and PD-L2) on PC cells is highly variable, therapy with enzalutamide can upregulate PD-L1 expression in the tumour microenvironment; this can represent a mechanism of resistance by inducing immune evasion [73].

In the phase Ib Keynote-028 and phase II Keynote-199 trials, mCRPC enzalutamide-refractory patients and previous untreated patients received the combination of pembrolizumab and enzalutamide, reaching potentially enhanced and durable response rates [74,75]. Based on these premises, the ongoing randomized, double-blind, placebo-controlled, phase III KEYNOTE-991 (NCT04191096) [76] is investigating if this combination therapy in NHA-naive participants with mHSPC is superior to enzalutamide plus placebo. Stratification by prior docetaxel therapy and the presence of high-volume disease is planned. Pembrolizumab 200 mg every three weeks will be administered for up to 35 cycles, loss of clinical benefit or intolerable AEs. The two co-primary endpoints are OS and rPFS. Archival or newly obtained tumour tissue and blood for genetic, RNA, serum, and plasma biomarkers and ctDNA analyses will be collected from all participants to support exploratory analyses of novel biomarkers. PROSTRATEGY (NCT03879122) is another phase III clinical trial that is investigating the role of immunotherapy in high-volume mHSPC [77]. This trial will randomise approximately 135 patients in three arms: ADT + docetaxel for 6 cycles (control arm, ARM 1); ADT + docetaxel for 6 cycles and then nivolumab 3 mg/kg every two weeks for 12 months (ARM 2); ADT + 2 cycles of ipilimumab 3 mg/kg every 3 weeks, followed by 3 cycles of docetaxel, 2 cycles of ipilimumab, 3 cycles of docetaxel, and then nivolumab 3 mg/kg every two weeks for 12 months (ARM 3). The primary endpoint is OS.

4.2. Radiopharmaceuticals

Lutetium-177(177Lu)-PSMA-617 is a beta emitter radioisotopic agent approved by FDA in 2022 for the treatment of mCRPC in patients who had progressed to an NHA and a taxane-based chemotherapy, and whose metastatic lesions express the prostatic-specific membrane antigen (PSMA) as documented by PSMA imaging [78]. Radiopharmaceuticals release alpha or beta radiations to cancer cells thought radioisotopes; radiations activate apoptosis by single- and double-strand DNA breaks [79]. PSMAddition (NCT04720157) [80] is a phase III, randomized, open-label, international, prospective clinical trial that aims to evaluate the efficacy and safety of 177Lu-PSMA-617 in combination with SOC (ADT plus NHA), versus SOC alone, in mHSPC. About 1126 patients will be randomized 1:1 to receive the SOC, with or without 177Lu-PSMA-617 administered once every 6 weeks for six cycles. Exclusion criteria is a rapidly progressing tumour that requires chemotherapy. The primary endpoint is rPFS. Stratification according to age (≥70 years/<70 years), high-volume vs. low-volume disease and previous/planned prostatectomy or radiation treatment of the primary prostate tumour is planned.

4.3. Molecular target agents

The role of molecular target agents has been largely investigated in the mCRPC setting in combination with ADT. The increase in knowledge of the mutational profile in mHSPC is leading to test targeted treatments, such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, poly(ADP-ribose) polymerase inhibitors (PARPi), and AKT-inhibitors (AKTi), also in this setting [81].

4.3.1. CDK4/6 inhibitors

During G1-S checkpoint, CDK4/6 activation by AR axis contributes to cancer cell proliferation; among mechanisms of resistance to NHA, upregulation of cyclin D1 (whose association with CDK4/6 is crucial for transition from G1 to S phase) has been described [82]. CYCLONE-03 (NCT05288166) [83] is a placebo-controlled phase III study that will randomise about 900 patients affected by high-risk NHA-naïve mHSPC (defined by at least 4 bone metastasis and/or visceral disease) to receive either abemaciclib (a selective CDK4/6 inhibitor) or placebo, plus abiraterone and prednisone. Visceral metastases and *de novo* mHSPC are stratification factors. The primary endpoint is rPFS.

4.3.2. PARP inhibitors

Preclinical and clinical data have showed that co-inhibition of AR axis and PARP induces a combined anti-tumour effect: PARP is involved in positive co-regulation of AR signalling, so

 doi:10.20944/preprints202309.0633.v1

PARP/AR signalling co-inhibition leads to enhanced AR target gene suppression; moreover, treatment with NHAs inhibits the transcription of some DDR genes, inducing synthetic lethality by cancer cells' inability to repair DNA even in patients without any DDR alterations [84]. The combination of the PARPi olaparib with abiraterone is FDA and EMA approved as first-line treatment of mCRPC, if chemotherapy is not clinically indicated, according to the results of PROPEL [85]. The combination of the PARPi talazoparib and enzalutamide has been recently FDA approved as first-line treatment of patients with homologous recombination repair (HRR) gene-mutated mCRPC according to TALAPRO-2 [86]. TALAPRO-3 (NCT04821622) [87] is a randomized double-blind trial that has recruited 599 men with mHSPC and HRR-related genes alterations (*ATM, ART, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*) to receive enzalutamide in association with placebo or talazoparib. The primary endpoint is rPFS. Patients will be stratified according to non-*BRCA* vs. *BRCA* alteration, low-volume vs. high volume disease, *de novo* vs. metachronous mHSPC. Similarly, the randomized, placebo controlled, double-blind trial AMPLITUDE (NCT04497844) [88] will enrol approximately 692 patients with mHSPC and HRR alterations to receive the PARPi niraparib or placebo in combination with abiraterone. The primary endpoint is rPFS. Patients will be stratified according to disease volume, previous docetaxel-based chemotherapy, and the type of HRR-related gene defect.

4.3.3. AKT inhibitors

Inactivation of the tumour suppressor gene *PTEN* by deletion or mutation is frequent in PC, especially in late-stage tumours. Loss of PTEN function leads to PI3K/AKT signalling pathway activation and suppression of AR transcriptional output. AKTi activate AR signalling, suggesting potential efficacy of the inhibition of both PI3K and AR signalling pathways [89]. Evidence supporting this association comes from the phase III trial IPATential150 [90] that demonstrated that the AKTi ipatasertib, in association with abiraterone, improve rPFS in patients with mCRPC and PTEN-loss. CAPItello-281 (NCT04493853) [91], a randomized double-blind trial, will test the AKTi capivasertib. Approximately 1000 patients with mHSPC PTEN-deficient, demonstrated on tissue immunohistochemistry, will be randomized 1:1 to receive capivasertib or placebo in association with abiraterone. The primary endpoint is rPFS.

5. Conclusions

The road towards a personalized treatment for *de novo* mHSPC is still long considering that the randomized clinical trials, which have furnished the basis of the current therapeutic options, stratified patients according to clinical criteria that not necessarily reflect the biological rationale of the chosen therapy. Transcriptomic profiling of mHSPC has revealed a predominance of aggressive and poor prognosis subtypes, but its role as a predictive biomarker requires further validation. Even though many of the genomic alterations detected in mHSPC are considered predictive in mCRPC, it remains to ascertain how these alterations can be exploited in the mHSPC field. In this sense, the ProBio (NCT03903835) trial, that is randomizing both mHSPC and mCRPC to receive SOC following national guidelines (control arm) or treatments based on a biomarker signature inferred from diagnostic tissue or liquid biopsy profiling (experimental arm), will probably furnish prospective evaluation of biomarker-driven treatments.

Author Contributions: Conceptualization, C.P. and M.G.V.; writing—original draft preparation, C.P., O.M., E.T., M.P., R.M.; writing—review and editing, C.P.; supervision, C.B., S.P., M.D., M.G.V. and R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Prostate – Global Cancer Observatory. Available online: https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf (accessed on 7 August 2023)
2. Helgstrand, J.T.; Røder, M.A.; Klemann, N.; Toft, B.G.; Lichtensztajn, D.Y.; Brooks, J.D.; Brasso, K.; Vainer, B.; Iversen, P. Trends in incidence and 5-year mortality in men with newly diagnosed, metastatic prostate cancer – A population-based analysis of 2 national cohorts. *Cancer* **2018**, *124*, 2931-2938, doi: 10.1002/cncr.31384.
3. Buzzoni, C.; Auvinen, A.; Roobol, M.J.; Carlsson, S.; Moss, S.M.; Puliti, D.; de Koning, H.J.; Bangma, C.H.; Denis, L.J.; Kwiatkowski, M.; et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: new insights from the European Randomized Study of Screening for Prostate Cancer. *Eur Urol* **2015**, *68*, 885-890, doi: 10.1016/j.eururo.2015.02.042.
4. Weiner, A.B.; Matulewicz, R.S.; Eggener, S.E.; Schaeffer, E.M. Increasing incidence of metastatic prostate cancer in the United States (2004–2013). *Prostate Cancer Prostat Dis* **2016**, *19*, 395-397, doi: 10.1038/pcan.2016.30.
5. Hu, J.C.; Nguyen, P.; Mao, J.; Halpern, J.; Shoag, J.; Wright, J.D.; Sedrakyan, A. Increase in Prostate Cancer Distant Metastases at Diagnosis in the United States. *JAMA Oncol* **2017**, *3*, 705-707, doi: 10.1001/jamaoncol.2016.5465.
6. Perera, M.; Papa, N.; Roberts, M.; Williams, M.; Udovicich, C.; Vela, I.; Christidis, D.; Bolton, D.; Hofman, M.S.; Lawrentschuk, N.; et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol* **2020**, *77*, 403-417, doi: 10.1016/j.eururo.2019.01.049.
7. Finianos, A.; Gupta, K.; Clark, B.; Simmens, S.J.; Aragon-Ching, J.B. Characterization of Differences Between Prostate Cancer Patients Presenting With De Novo Versus Primary Progressive Metastatic Disease. *Clin Genitourin Cancer* **2017**, *S1558-7673*, 30247-1, doi: 10.1016/j.clgc.2017.08.006.
8. Sweeney, C.J.; Chen, Y.H.; Carducci, M.; Liu, G.; Jarrard, D.F.; Eisenberger, M.; Wong, Y.N.; Hahn, N.; Kohli, M.; Cooney, M.M.; et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* **2015**, *373*, 737-746, doi: 10.1056/NEJMoa1503747. CHAARTED
9. James, N.D.; Sydes, M.R.; Clarke, N.W.; Mason, M.D.; Dearnaley, D.P.; Spears, M.R.; Ritchie, A.W.; Parker, C.C.; Russell, J.M.; Attard, G.; et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* **2016**, *387*, 1163-1177, doi: 10.1016/S0140-6736(15)01037-5.
10. Fizazi, K.; Tran, N.; Fein, L.; Matsubara, N.; Rodriguez-Antolin, A.; Alekseev, B.Y.; Özgüroğlu, M.; Ye, D.; Feyerabend, S.; Protheroe, A.; et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* **2017**, *377*, 352-360, doi: 10.1056/NEJMoa1704174. LATITUDE
11. James, N.D.; de Bono, J.S.; Spears, M.R.; Clarke, N.W.; Mason, M.D.; Dearnaley, D.P.; Ritchie, A.W.S.; Amos, C.L.; Gilson, C.; Jones, R.J.; et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* **2017**, *377*, 338-351, doi: 10.1056/NEJMoa1702900. STAMPEDE
12. Davis, I.D.; Martin, A.J.; Stockler, M.R.; Begbie, S.; Chi, K.N.; Chowdhury, S.; Coskinas, X.; Frydenberg, M.; Hague, W.E.; Horvath, L.G.; et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* **2019**, *381*, 121-131, doi: 10.1056/NEJMoa1903835. ENZAMET
13. Armstrong, A.J.; Szmulewitz, R.Z.; Petrylak, D.P.; Holzbeierlein, J.; Villers, A.; Azad, A.; Alcaraz, A.; Alekseev, B.; Iguchi, T.; Shore, N.D.; et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* **2019**, *37*, 2974-2986, doi: 10.1200/JCO.19.00799.
14. Chi, K.N.; Agarwal, N.; Bjartell, A.; Chung, B.H.; Pereira de Santana Gomes, A.J.; Given, R.; Juárez Soto, Á.; Merseburger, A.S.; Özgüroğlu, M.; Uemura, H.; et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* **2019**, *381*, 13-24, doi: 10.1056/NEJMoa1903307. TITAN
15. Kyriakopoulos, C.E.; Chen, Y.H.; Carducci, M.A.; Liu, G.; Jarrard, D.F.; Hahn, N.M.; Shevrin, D.H.; Dreicer, R.; Hussain, M.; Eisenberger, M.; et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol* **2018**, *36*, 1080-1087, doi: 10.1200/JCO.2017.75.3657.
16. Hamid, A.A.; Huang, H.C.; Wang, V.; Chen, Y.H.; Feng, F.; Den, R.; Attard, G.; Van Allen, E.M.; Tran, P.T.; Spratt, D.E.; et al. Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive

prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial. *Ann Oncol* **2021**, *32*, 1157-1166, doi: 10.1016/j.annonc.2021.06.003.

17. Spratt, D.E.; Yousefi, K.; Deheshi, S.; Ross, A.E.; Den, R.B.; Schaeffer, E.M.; Trock, B.J.; Zhang, J.; Glass, A.G.; Dicker, A.P.; et al. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. *J Clin Oncol* **2017**, *35*, 1991-1998, doi: 10.1200/JCO.2016.70.2811.
18. Zhao, S.G.; Chang, S.L.; Erho, N.; Yu, M.; Lehrer, J.; Alshalalfa, M.; Speers, C.; Cooperberg, M.R.; Kim, W.; Ryan, C.J.; et al. Associations of Luminal and Basal Subtyping of Prostate Cancer With Prognosis and Response to Androgen Deprivation Therapy. *JAMA Oncol* **2017**, *3*, 1663-1672, doi: 10.1001/jamaoncol.2017.0751.
19. Spratt, D.E.; Alshalalfa, M.; Fishbane, N.; Weiner, A.B.; Mehra, R.; Mahal, B.A.; Lehrer, J.; Liu, Y.; Zhao, S.G.; Speers, C.; et al. Transcriptomic Heterogeneity of Androgen Receptor Activity Defines a *de novo* low AR-Active Subclass in Treatment Naïve Primary Prostate Cancer. *Clin Cancer Res* **2019**, *25*, 6721-6730. doi: 10.1158/1078-0432.CCR-19-1587.
20. Fizazi, K.; Tran, N.; Fein, L.; Matsubara, N.; Rodriguez-Antolin, A.; Alekseev, B.Y.; Özgüroğlu, M.; Ye, D.; Feyerabend, S.; Protheroe, A.; et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol* **2019**, *20*, 686-700, doi: 10.1016/S1470-2045(19)30082-8.
21. Roy, S.; Sun, Y.; Wallis, C.J.D.; Morgan, S.C.; Grimes, S.; Malone, J.; Kishan, A.U.; Mukherjee, D.; Spratt, D.E.; Saad, F.; Malone S. Development and validation of a multivariable prognostic model in de novo metastatic castrate sensitive prostate cancer. *Prostate Cancer Prostatic Dis* **2023**, *26*, 119-125, doi: 10.1038/s41391-022-00560-3.
22. Azad, A.A.; Armstrong, A.J.; Alcaraz, A.; Szmulewitz, R.Z.; Petrylak, D.P.; Holzbeierlein, J.; Villers, A.; Alekseev, B.; Iguchi, T.; Shore, N.D.; et al. Efficacy of enzalutamide in subgroups of men with metastatic hormone-sensitive prostate cancer based on prior therapy, disease volume, and risk. *Prostate Cancer Prostatic Dis* **2022**, *25*, 274-282, doi: 10.1038/s41391-021-00436-y.
23. Azad, A.A.; Villers, A.; Alekseev, B.; Szmulewitz, R.Z.; Alcaraz, A.; Shore, N.D.; Petrylak, D.P.; Holzbeierlein, J.; Gomez-Veiga, F.; Rosbrook, B.; et al. Efficacy of enzalutamide (ENZA) plus androgen deprivation therapy (ADT) in men with *de novo* (M1) metastatic hormone-sensitive prostate cancer (mHSPC) versus progression to mHSPC (M0): Post hoc analysis of the phase III ARCHES trial. *J Clin Oncol* **2021**, *39*, 6_suppl, doi: 10.1200/JCO.2021.39.6_suppl.102.
24. Armstrong, A.J.; Azad, A.A.; Iguchi, T.; Szmulewitz, R.Z.; Petrylak, D.P.; Holzbeierlein, J.; Villers, A.; Alcaraz, A.; Alekseev, B.; Shore, N.D.; et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol* **2022**, *40*, 1616-1622, doi: 10.1200/JCO.22.00193.
25. Sweeney, C.J.; Martin, A.J.; Stockler, M.R.; Begbie, S.; Cheung, L.; Chi, K.N.; Chowdhury, S.; Frydenberg, M.; Horvath, L.G.; Joshua, A.M.; et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* **2023**, *24*, 323-334, doi: 10.1016/S1470-2045(23)00063-3.
26. Chi, K.N.; Chowdhury, S.; Bjartell, A.; Chung, B.H.; Pereira de Santana Gomes, A.J.; Given, R.; Juárez, A.; Merseburger, A.S.; Özgüroğlu, M.; Uemura, H.; et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. *J Clin Oncol* **2021**, *39*, 2294-2303, doi: 10.1200/JCO.20.03488.
27. Feng, F.Y.; Thomas, S.; Aguilar-Bonavides, C.; Gormley, M.; Agarwal, N.; Attard, G.; Wyatt, A.W.; Davicioni, E.; Ricci, D.S.; Lopez-Gitlitz, A.; et al. Molecular determinants of outcome for metastatic castration-sensitive prostate cancer (mCSPC) with addition of apalutamide (APA) or placebo (PBO) to androgen deprivation therapy (ADT) in TITAN. *J Clin Oncol* **2020**, *38*, suppl 15, 5535-5535, doi: 10.1200/JCO.2020.38.15_suppl.5535
28. Feng, F.Y.; Thomas, S.; Saad, F.; Gormley, M.; Yu, M.K.; Ricci, D.S.; Rooney, B.; Brookman-May, S.; McCarthy, S.; Olmos, D.; et al. Association of Molecular Subtypes With Differential Outcome to Apalutamide Treatment in Nonmetastatic Castration-Resistant Prostate Cancer. *JAMA Oncol* **2021**, *7*, 1005-1014, doi: 10.1001/jamaoncol.2021.1463.

29. Agarwal, N.; Lucas, J.; Aguilar-Bonavides, C.; Thomas, S.; Gormley, M.; Chowdhury, S.; Merseburger, A.S.; Bjartell, A.; Uemura, H.; Özgüroğlu, M.; et al. Genomic aberrations associated with overall survival (OS) in metastatic castration-sensitive prostate cancer (mCSPC) treated with apalutamide (APA) or placebo (PBO) plus androgen deprivation therapy (ADT) in TITAN. *J Clin Oncol* **2022**, *40*, suppl 16, 5066-5066, doi: 10.1200/JCO.2022.40.16_suppl.5066.
30. Smith, M.R.; Hussain, M.; Saad, F.; Fizazi, K.; Sternberg, C.N.; Crawford, E.D.; Kopyltsov, E.; Park, C.H.; Alekseev, B.; Montesa-Pino, Á.; et al. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med* **2022**, *386*, 1132-1142, doi: 10.1056/NEJMoa2119115. ARASENS
31. Hussain, M.; Tombal, B.; Saad, F.; Fizazi, K.; Sternberg, C.N.; Crawford, E.D.; Shore, N.; Kopyltsov, E.; Kalebasty, A.R.; Bögemann, M.; et al. Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial. *J Clin Oncol* **2023**, *41*, 3595-3607, doi: 10.1200/JCO.23.00041.
32. Fizazi, K.; Foulon, S.; Carles, J.; Roubaud, G.; McDermott, R.; Fléchon, A.; Tombal, B.; Supiot, S.; Berthold, D.; Ronchin, P.; et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with 2 × 2 factorial design. *Lancet* **2022**, *399*, 1695-1707, doi: 10.1016/S0140-6736(22)00367-1.
33. Katipally, R.R.; Pitroda, S.P.; Juloori, A.; Chmura, S.J.; Weichselbaum, R.R. The oligometastatic spectrum in the era of improved detection and modern systemic therapy. *Nat Rev Clin Oncol* **2022**, *19*, 585-599, doi: 10.1038/s41571-022-00655-9.
34. Mahjoub, S.; Heidenreich, A. Oligometastatic prostate cancer: definition and the role of local and systemic therapy: a narrative review. *Transl Androl Urol* **2021**, *10*, 3167-3175, doi: 10.21037/tau-20-1033.
35. Singh, D.; Yi, W.S.; Brasacchio, R.A.; Muhs, A.G.; Smudzin, T.; Williams, J.P.; Messing, E.; Okunieff, P. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys* **2004**, *58*, 3-10, doi: 10.1016/s0360-3016(03)01442-1.
36. Gravis, G.; Fizazi, K.; Joly, F.; Oudard, S.; Priou, F.; Esterni, B.; Latorzeff, I.; Delva, R.; Krakowski, I.; Laguerre, B.; et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* **2013**, *14*, 149-158, doi: 10.1016/S1470-2045(12)70560-0.
37. Gravis, G.; Boher, J.M.; Chen, Y.H.; Liu, G.; Fizazi, K.; Carducci, M.A.; Oudard, S.; Joly, F.; Jarrard, D.M.; Soulie, M.; et al. Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies. *Eur Urol* **2018**, *73*, 847-855, doi: 10.1016/j.eururo.2018.02.001.
38. Hoyle, A.P.; Ali, A.; James, N.D.; Cook, A.; Parker, C.C.; de Bono, J.S.; Attard, G.; Chowdhury, S.; Cross, W.R.; Dearnaley, D.P.; et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. *Eur Urol* **2019**, *76*, 719-728, doi: 10.1016/j.eururo.2019.08.006.
39. Boevé, L.M.S.; Hulshof, M.C.C.M.; Vis, A.N.; Zwinderman, A.H.; Twisk, J.W.R.; Witjes, W.P.J.; Delaere, K.P.J.; Moorselaar, R.J.A.V.; Verhagen, P.C.M.S.; van Andel, G. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. *Eur Urol* **2019**, *75*, 410-418, doi: 10.1016/j.eururo.2018.09.008.
40. Parker, C.C.; James, N.D.; Brawley, C.D.; Clarke, N.W.; Hoyle, A.P.; Ali, A.; Ritchie, A.W.S.; Attard, G.; Chowdhury, S.; Cross, W.; et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* **2018**, *392*, 2353-2366, doi: 10.1016/S0140-6736(18)32486-3.
41. Dai, B.; Zhang, S.; Wan, F.N.; Wang, H.K.; Zhang, J.Y.; Wang, Q.F.; Kong, Y.Y.; Ma, X.J.; Mo, M.; Zhu, Y.; et al. Combination of Androgen Deprivation Therapy with Radical Local Therapy Versus Androgen Deprivation Therapy Alone for Newly Diagnosed Oligometastatic Prostate Cancer: A Phase II Randomized Controlled Trial. *Eur Urol Oncol* **2022**, *5*, 519-525, doi: 10.1016/j.euo.2022.06.001.
42. Bossi, A.; Foulon, S.; Maldonado, X.; Sargos, P.; McDermott, R.S.; Flechon, A.; Tombal, B.F.; Supiot, S.; Berthold, D.R.; Ronchin, P.; et al. Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2 × 2 design. *J Clin Oncol* **2023**, *41*, LBA5000-LBA5000, doi: 10.1200/JCO.2023.41.17_suppl.LBA5000.

43. Parker, C.; Castro, E.; Fizazi, K.; Heidenreich, A.; Ost, P.; Procopio, G.; Tombal, B.; Gillessen, S.; ESMO Guidelines Committee. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **2020**, *31*, 1119-1134, doi: 10.1016/j.annonc.2020.06.011.
44. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 3.2023 – August 7, 2023.
45. Ost, P.; Reynders, D.; Decaestecker, K.; Fonteyne, V.; Lumen, N.; De Bruycker, A.; Lambert, B.; Delrue, L.; Bultijnck, R.; Claeys, T.; et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* **2018**, *36*, 446-453, doi: 10.1200/JCO.2017.75.4853. STOMP
46. Phillips, R.; Shi, W.Y.; Deek, M.; Radwan, N.; Lim, S.J.; Antonarakis, E.S.; Rowe, S.P.; Ross, A.E.; Gorin, M.A.; Deville, C.; et al. Outcomes of Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* **2020**, *6*, 650-659, doi: 10.1001/jamaoncol.2020.0147.
47. Gillessen, S.; Bossi, A.; Davis, I.D.; de Bono, J.; Fizazi, K.; James, N.D.; Mottet, N.; Shore, N.; Small, E.; Smith, M.; et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. *Eur J Cancer* **2023**, *185*, 178-215, doi: 10.1016/j.ejca.2023.02.018.
48. O'Shaughnessy, M.J.; McBride, S.M.; Vargas, H.A.; Touijer, K.A.; Morris, M.J.; Danila, D.C.; Laudone, V.P.; Bochner, B.H.; Sheinfeld, J.; Dayan, E.S.; et al. A Pilot Study of a Multimodal Treatment Paradigm to Accelerate Drug Evaluations in Early-stage Metastatic Prostate Cancer. *Urology* **2017**, *102*, 164-172, doi: 10.1016/j.urology.2016.10.044.
49. Reyes, D.K.; Rowe, S.P.; Schaeffer, E.M.; Allaf, M.E.; Ross, A.E.; Pavlovich, C.P.; Deville, C.; Tran, P.T.; Pienta, K.J. Multidisciplinary total eradication therapy (TET) in men with newly diagnosed oligometastatic prostate cancer. *Med Oncol* **2020**, *37*, 60, doi: 10.1007/s12032-020-01385-7.
50. Reyes, D.K.; Trock, B.J.; Tran, P.T.; Pavlovich, C.P.; Deville, C.; Allaf, M.E.; Greco, S.C.; Song, D.Y.; Bivalacqua, T.J.; Han, M.; et al. Interim analysis of companion, prospective, phase II, clinical trials assessing the efficacy and safety of multi-modal total eradication therapy in men with synchronous oligometastatic prostate cancer. *Med Oncol* **2022**, *39*, 63, doi: 10.1007/s12032-022-01662-7.
51. Deantoni, C.L.; Fodor, A.; Cozzarini, C.; Fiorino, C.; Brombin, C.; Di Serio, C.; Calandrino, R.; Di Muzio, N. Prostate cancer with low burden skeletal disease at diagnosis: outcome of concomitant radiotherapy on primary tumor and metastases. *Br J Radiol* **2020**, *93*, 20190353, doi: 10.1259/bjr.20190353.
52. Nabrinsky, E.; Macklis, J.; Bitran, J. A Review of the Abscopal Effect in the Era of Immunotherapy. *Cureus* **2022**, *14*, e29620, doi: 10.7759/cureus.29620.
53. Gundem, G.; Van Loo, P.; Kremeyer, B.; Alexandrov, L.B.; Tubio, J.M.C.; Papaemmanuil, E.; Brewer, D.S.; Kallio, H.M.L.; Högnäs, G.; Annala, M.; et al. The evolutionary history of lethal metastatic prostate cancer. *Nature* **2015**, *520*, 353-357, doi: 10.1038/nature14347.
54. Dorpe, J.; Fonteyne, V.; et al. Tissue- and Blood-derived Genomic Biomarkers for Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review. *Eur Urol Oncol* **2021**, *4*, 914-923, doi: 10.1016/j.euo.2021.10.005.
55. Deek, M.P.; Van der Eecken, K.; Phillips, R.; Parikh, N.R.; Isaacsson Velho, P.; Lotan, T.L.; Kishan, A.U.; Maurer, T.; GAP6 Consortium; Boutros, P.C. The Mutational Landscape of Metastatic Castration-sensitive Prostate Cancer: The Spectrum Theory Revisited. *Eur Urol* **2021**, *80*, 632-640, doi: 10.1016/j.eururo.2020.12.040.
56. Deek, M.P.; Van der Eecken, K.; Sutera, P.; Deek, R.A.; Fonteyne, V.; Mendes, A.A.; Decaestecker, K.; Kiess, A.P.; Lumen, N.; Phillips, R.; et al. Long-Term Outcomes and Genetic Predictors of Response to Metastasis-Directed Therapy Versus Observation in Oligometastatic Prostate Cancer: Analysis of STOMP and ORIOLE Trials. *J Clin Oncol* **2022**, *40*, 3377-3382, doi: 10.1200/JCO.22.00644.Van der Eecken, K.; Vanwelkenhuyzen, J.; Deek, M.P.; Tran, P.T.; Warner, E.; Wyatt, A.W.; Kwan, E.M.; Verbeke, S.; Van
57. Armenia, J.; Wankowicz, S.A.M.; Liu, D.; Gao, J.; Kundra, R.; Reznik, E.; Chatila, W.K.; Chakravarty, D.; Han, G.C.; Coleman, I.; et al. The long tail of oncogenic drivers in prostate cancer. *Nat Genet* **2018**, 50, 645-651, doi: 10.1038/s41588-018-0078-z.
58. Chung, J.H.; Dewal, N.; Sokol, E.; Mathew, P.; Whitehead, R.; Millis, S.Z.; Frampton, G.M.; Bratslavsky, G.; Pal, S.K.; Lee, R.J.; et al. Prospective Comprehensive Genomic Profiling of Primary and Metastatic Prostate Tumors. *JCO Precis Oncol* **2019**, *3*, PO.18.00283, doi: 10.1200/PO.18.00283.

59. Kumar, A.; White, T.A.; MacKenzie, A.P.; Clegg, N.; Lee, C.; Dumpit, R.F.; Coleman, I.; Ng, S.B.; Salipante, S.J.; Rieder, M.J.; et al. Exome sequencing identifies a spectrum of mutation frequencies in advanced and lethal prostate cancers. *Proc Natl Acad Sci U S A* **2011**, *108*, 17087-92, doi: 10.1073/pnas.1108745108.
60. Abida, W.; Armenia, J.; Gopalan, A.; Brennan, R.; Walsh, M.; Barron, D.; Danila, D.; Rathkopf, D.; Morris, M.; Slovin, S.; et al. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. *JCO Precis Oncol* **2017**, *2017*, PO.17.00029, doi: 10.1200/PO.17.00029.
61. Hamid, A.A.; Gray, K.P.; Shaw, G.; MacConaill, L.E.; Evan, C.; Bernard, B.; Loda, M.; Corcoran, N.M.; Van Allen, E.M.; Choudhury, A.D.; et al. Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. *Eur Urol* **2019**, 76, 89-97, doi: 10.1016/j.eururo.2018.11.045.
62. Gilson, C.; Ingleby, F.; Gilbert, D.C.; Parry, M.A.; Atako, N.B.; Ali, A.; Hoyle, A.; Clarke, N.W.; Gannon, M.; Wanstall, C.; et al. Genomic Profiles of De Novo High- and Low-Volume Metastatic Prostate Cancer: Results From a 2-Stage Feasibility and Prevalence Study in the STAMPEDE Trial. *JCO Precis Oncol* **2020**, *4*, 882-897, doi: 10.1200/PO.19.00388.
63. Vandekerkhove, G.; Struss, W.J.; Annala, M.; Kallio, H.M.L.; Khalaf, D.; Warner, E.W.; Herberts, C.; Ritch, E.; Beja, K.; Loktionova, Y.; et al. Circulating Tumor DNA Abundance and Potential Utility in De Novo Metastatic Prostate Cancer. *Eur Urol* **2019**, *75*, 667-675, doi: 10.1016/j.eururo.2018.12.042.
64. Fan, L.; Fei, X.; Zhu, Y.; Pan, J.; Sha, J.; Chi, C.; Gong, Y.; Du, X.; Zhou, L.; Dong, B.; et al. Comparative Analysis of Genomic Alterations across Castration Sensitive and Castration Resistant Prostate Cancer via Circulating Tumor DNA Sequencing. *J Urol* **2021**, *205*, 461-469, doi: 10.1097/JU.0000000000001363.
65. Kohli, M.; Tan, W.; Zheng, T.; Wang, A.; Montesinos, C.; Wong, C.; Du, P.; Jia, S.; Yadav, S.; Horvath, L.G.; et al. Clinical and genomic insights into circulating tumor DNA-based alterations across the spectrum of metastatic hormone-sensitive and castrate-resistant prostate cancer. *EbioMedicine* **2020**, *54*, 102728, doi: 10.1016/j.ebiom.2020.102728.
66. Trujillo, B.; Wu, A.; Wetterskog, D.; Attard, G. Blood-based liquid biopsies for prostate cancer: clinical opportunities and challenges. *Br J Cancer* **2022**, *127*, 1394-1402, doi: 10.1038/s41416-022-01881-9.
67. Stopsack, K.H.; Nandakumar, S.; Wibmer, A.G.; Haywood, S.; Weg, E.S.; Barnett, E.S.; Kim, C.J.; Carbone, E.A.; Vasselman, S.E.; Nguyen, B.; et al. Oncogenic genomic alterations, clinical phenotypes, and outcomes in metastatic castration-sensitive prostate cancer. *Clin Cancer Res* **2020**, *26*, 3230-3238, doi: 10.1158/1078-0432.CCR-20-0168.
68. Velez, M.G.; Kosiorek, H.E.; Egan, J.B.; McNatty, A.L.; Riaz, I.B.; Hwang, S.R.; Stewart, G.A.; Ho, T.H.; Moore, C.N.; Singh, P.; et al. Differential impact of tumor suppressor gene (TP53, PTEN, RB1) alterations and treatment outcomes in metastatic, hormone-sensitive prostate cancer. *Prostate Cancer Prostatic Dis* **2022**, 25, 479-483. doi: 10.1038/s41391-021-00430-4.
69. Mateo, J.; Seed, G.; Bertan, C.; Rescigno, P.; Dolling, D.; Figueiredo, I.; Miranda, S.; Nava Rodrigues, D.; Gurel, B.; Clarke, M.; et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. *J Clin Invest* **2020**, 130, 1743-1751, doi: 10.1172/JCI132031.
70. Swami, U.; Isaacsson Velho, P.; Nussenzveig, R.; Chipman, J.; Sacristan Santos, V.; Erickson, S.; Dharmaraj, D.; Alva, A.S.; Vaishampayan, U.N.; Esther, J.; et al. Association of SPOP Mutations with Outcomes in Men with De Novo Metastatic Castration-sensitive Prostate Cancer. *Eur Urol* **2020**, *78*, 652-656, doi: 10.1016/j.eururo.2020.06.033.
71. Wang, Z.; Song, Y.; Ye, M.; Dai, X.; Zhu, X.; Wei, W. The diverse roles of SPOP in prostate cancer and kidney cancer. *Nat Rev Urol* **2020**, *17*, 339-350, doi: 10.1038/s41585-020-0314-z.
72. Swami, U.; Graf, R.P.; Nussenzveig, R.H.; Fisher, V.; Tukachinsky, H.; Schrock, A.B.; Li, G.; Ross, J.S.; Sayegh, N.; Tripathi, N.; et al. SPOP Mutations as a Predictive Biomarker for Androgen Receptor Axis-Targeted Therapy in De Novo Metastatic Castration-Sensitive Prostate Cancer. *Clin Cancer Res* **2022**, *28*, 4917-4925, doi: 10.1158/1078-0432.CCR-22-2228.
73. Bishop, J.L.; Sio, A.; Angeles, A.; Roberts, M.E.; Azad, A.A.; Chi, K.N.; Zoubeidi, A. PD-L1 is highly expressed in Enzalutamide resistant prostate cancer. *Oncotarget* **2015**, *6*, 234-242, doi: 10.18632/oncotarget.2703.
74. Graff, J.N.; Beer, T.M.; Alumkal, J.J.; Slottke, R.E.; Redmond, W.L.; Thomas, G.V.; Thompson, R.F.; Wood, M.A.; Koguchi, Y.; Chen, Y.; et al. A phase II single-arm study of pembrolizumab with enzalutamide in

men with metastatic castration-resistant prostate cancer progressing on enzalutamide alone. *J Immunother Cancer* **2020**, *8*, e000642, doi: 10.1136/jitc-2020-000642.

75. Lin, H.; Liu, Q.; Zeng, X.; Yu, W.; Xu, G. Pembrolizumab with or without enzalutamide in selected populations of men with previously untreated metastatic castration-resistant prostate cancer harbouring programmed cell death ligand-1 staining: a retrospective study. *BMC Cancer* **2021**, *21*, 399, doi: 10.1186/s12885-021-08156-1.
76. Gratzke, C.; Kwiatkowski, M.; De Giorgi, U.; Martins da Trindade, K.; De Santis, M.; Armstrong, A.J.; Niu, C.; Liu, Y.; Poehlein, C.H. KEYNOTE-991: pembrolizumab plus enzalutamide and androgen deprivation for metastatic hormone-sensitive prostate cancer. *Future Oncol* **2023** Jan 27, doi: 10.2217/fon-2022-0776. Epub ahead of print.
77. Arranz Arija, J. A.; Valderrama, B.P.; Alonso Gordoa, T.; Gallardo Diaz, E.; Sepulveda Sanchez, J. M.; Fernandez-Parra, E.; Piulats, J.M.; Mendez Vidal, M. J.; Sala González, N.; Vazquez Estevez, S.; et. al. PROSTRATEGY: A Spanish Genitourinary Oncology Group (SOGUG) multi-arm multistage (MAMS) phase III trial of immunotherapy strategies in high-volume metastatic hormone-sensitive prostate cancer. *Ann Oncol* **2019**, *30*, suppl_5, V352-V353, doi:10.1093/annonc/mdz248.051.
78. Fallah, J.; Agrawal, S.; Gittleman, H.; Fiero, M.H.; Subramaniam, S.; John, C.; Chen, W.; Ricks, T.K.; Niu, G.; Fotenos, A.; et al. FDA Approval Summary: Lutetium Lu 177 Vipivotide Tetraxetan for Patients with Metastatic Castration-Resistant Prostate Cancer. *Clin Cancer Res* **2023**, *29*, 1651-1657, doi: 10.1158/1078-0432.CCR-22-2875.
79. Núñez, M.I.; Villalobos, M.; Olea, N.; Valenzuela, M.T.; Pedraza, V.; McMillan, T.J.; Ruiz de Almodóvar, J.M. Radiation-induced DNA double-strand break rejoining in human tumour cells. *Br J Cancer* **1995**, *71*, 311-316. doi: 10.1038/bjc.1995.62.
80. Sartor, A.O.; Tagawa, S.T.; Saad, F.; De Bono, J.S.; Feng, F.Y.; Fizazi, K.; Sakharova, O.V.; Morris, M.J. PSMAddition: A phase 3 trial to compare treatment with 177Lu-PSMA-617 plus standard of care (SOC) versus SOC alone in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* **2022**, *40*, 6_suppl, TPS210-TPS210, doi: 10.1200/JCO.2022.40.6_suppl.TPS210.
81. Hamid, A.A.; Sayegh, N.; Tombal, B.; Hussain, M.; Sweeney C.J.; Graff J.N.; Agarwal N. Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment. Am Soc Clin Oncol Educ Book. **2023**, 5, doi: 10.1200/EDBK_390166.
82. Kase, A.M.; Copland III, J.A.; Tan, W. Novel Therapeutic Strategies for CDK4/6 Inhibitors in Metastatic Castrate-Resistant Prostate Cancer. *Onco Targets Ther* **2020**, *13*, 10499-10513, doi: 10.2147/OTT.S266085.
83. Smith, M.R.; Matsubara, N.; McKay, R.R.; Piulats, J.M.; Todenhöfer, T.; Zhang, T.; Fasnacht, N.; Sherwood, S.; Johnston, E.L.; Schaverien, C.; et a. CYCLONE 3: A phase III, randomized, double-blind, placebo-controlled study of abemaciclib in combination with abiraterone plus prednisone in men with high-risk metastatic hormone-sensitive prostate cancer (mHSPC), *J Clin Oncol* **2023**, *41*, 6_suppl:TPS289, doi: 10.1200/JCO.2023.41.6_suppl.TPS289.
84. Rao, A.; Moka, N.; Hamstra, D.A.; Ryan, C.J. Co-Inhibition of Androgen Receptor and PARP as a Novel Treatment Paradigm in Prostate Cancer-Where Are We Now? *Cancers (Basel)* **2022**, *14*, 801, doi: 10.3390/cancers14030801.
85. Clarke, N.W.; Armstrong, A.J.; Thiery-Vuillemin, A.; Oya, M.; Shore, N.; Loredo, E.; Procopio, G.; de Menezes, J.; Girotto, G.; Arslan, C.; et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. *NEJM Evid* **2022**, *1*, EVIDoa2200043, doi: 10.1056/EVIDoa2200043.
86. Agarwal, N.; Azad, A.A.; Carles, J.; Fay, A.P.; Matsubara, N.; Heinrich, D.; Szczylik, C.; De Giorgi, U.; Young Joung, J.; Fong, P.C.C.; et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet* **2023**, *402*, 291-303, doi: 10.1016/S0140-6736(23)01055-3.
87. Agarwal, N.; Saad, F.; Azad, A.; Mateo, J.; Matsubara, N.; Shore, N.D.; Chakrabarti, J.; Chen, H.; Lanzalone, S.; Niyazov, A.; et al. TALAPRO-3: A phase 3, double-blind, randomized study of enzalutamide (ENZA) plus talazoparib (TALA) vs. placebo plus ENZA in patients with DDR gene-mutated, metastatic castration-sensitive prostate cancer (mCSPC). *J Clin Oncol*, **2023**, *41*, 6_suppl, TPS279-TPS279, doi: 10.1200/JCO.2023.41.6_suppl.TPS279.
88. Rathkopf, D.E.; Chi, K.N.; Olmos, D.; Cheng, H.H.; Agarwal, N.; Graff, J.N.; Sandhu, S.K.; Hayreh, V.; Lopez-Gitlitz, A.; St. John Francis, P.; et al. AMPLITUDE: A study of niraparib in combination with abiraterone acetate plus prednisone (AAP) versus AAP for the treatment of patients with deleterious

germline or somatic homologous recombination repair (HRR) gene-altered metastatic castration-sensitive prostate cancer (mCSPC). *J Clin Oncol* **2021**, *3*, 39:6_suppl, TPS176, doi: 10.1200/JCO.2021.39.6_suppl.TPS176.

89. Jamaspishvili, T.; Berman, D.M.; Ross, A.E.; Scher, H.I.; De Marzo, A.M.; Squire, J.A.; Lotan, T.L. Clinical implications of PTEN loss in prostate cancer. *Nat Rev Urol* **2018**, *15*, 222-234, doi: 10.1038/nrurol.2018.9.
90. Sweeney, C.; Bracarda, S.; Sternberg, C.N.; Chi, K.N.; Olmos, D.; Sandhu, S.; Massard, C.; Matsubara, N.; Alekseev, B.; Parnis, F.; et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* **2021**, *398*, 131-142, doi: 10.1016/S0140-6736(21)00580-8.
91. Fizazi, K.; George, D.J.; De Santis, M.; Clarke, N.; Fay, A.P.; Uemura, H.; Grinsted, L.; Rooney, C.; Verheijen, R.B.; Anjum, R.; et al. A phase III trial of capivasertib and abiraterone versus placebo and abiraterone in patients with *de novo* metastatic hormone-sensitive prostate cancer characterized by PTEN deficiency (CAPItello-281). *J Clin Oncol* **2021**, *3*, 39, doi: 10.1200/JCO.2021.39.6_suppl.TPS178.