De Novo Metastatic Prostate Cancer Treatment

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

De novo metastatic hormone-sensitive prostate cancer usually has a dismal prognosis, which has slightly improved thanks to the introduction of new hormonal agents and chemotherapy combined with androgen deprivation therapy from the first-line setting. The randomized clinical trials that have furnished the current therapeutic options stratified patients according to clinical criteria that do 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 of defining a personalized treatment for de novo metastatic hormone-sensitive prostate cancer.

De novo metastatic hormone-sensitive prostate cancer | mHSPC | prostate cancer

1. Introduction

According to GLOBOCAN 2020, almost one and a half million new cases of prostate cancer (PC) and approximately 400.000 PC-related deaths were reported in 2020 globally [1]. De novo metastatic 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 increasing in Western countries, probably due to the introduction of new diagnostic tools in the imaging of PC, such as PSMA-PET, and a reduction in PSA opportunistic screening [4][5][6]. De novo mHSPC is characterized by an aggressive course with a briefer time of onset of castration resistance and worse overall survival (OS) in contrast with metachronous mHSPC [7]. Since 2015, the prognosis of mHSPC has slightly improved thanks to the introduction of new hormonal agents (NHAs) and chemotherapy, combined with androgen deprivation therapy (ADT) from the first-line setting [8][9][10][11][12][13][14]. Nonetheless, the current therapeutic decision making for 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) since clinical trials evaluating molecular-biomarker-guided treatment of mHSPC are still ongoing.

2. Current Therapeutic Opportunities for De Novo mHSPC

2.1. Doublet Therapy

2.1.1. Docetaxel Plus ADT

The first study that redefined the treatment paradigm for mHSPC was 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 patients 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 21 days for up to six cycles in association with ADT over ADT alone. After a median follow-up of 53.7 months, an absolute benefit in terms of the mOS of 16.8 months was observed in the experimental arm compared with 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 (as determined using the presence of at least four bone metastatic lesions with at least one beyond the vertebral bodies and pelvis and/or using evidence of visceral metastases), while no benefit was reported in men with low-volume mHSPC [15]. Transcriptional profiling of primary PC samples belonging to 160 men enrolled in this trial (of which 88% with synchronous mHSPC and 78% with high-volume disease) was performed by Hamid et al. [16] using the PAM50 classifier (luminal A, luminal B, and basal subtypes), the Decipher genomic classifier, and androgen receptor activity (AR-A, defined as average or lower) [17][18][19]. The analysis revealed a predominance of luminal B (50%) and basal (48%) subgroups, lower AR-A, and high Decipher risk tumors. The luminal B subgroup benefited significantly from the addition of docetaxel to ADT in terms of OS, while the basal subtype showed no OS advantage, even in the case of high-volume disease.

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, which was defined by at least two out of three risk factors (Gleason score ≥ 8, at least three bone metastatic lesions, and the evidence of visceral metastasis), were 1:1 randomized to be treated with abiraterone acetate plus prednisone (or prednisolone) plus ADT versus placebo plus ADT. Considering the notable advantage in terms of the radiological progression-free survival (rPFS) and OS observed in the experimental arm at an interim analysis, the trial was subsequently unblinded and crossover was allowed. At the final OS analysis (median follow-up 51.8 months), 72 patients had crossed over to abiraterone acetate from the control 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 control group (HR: 0.66, $p < 0.0001$) [20]. No analysis of predictive biomarkers of response to abiraterone acetate was reported.

2.1.3. Enzalutamide Plus ADT

The role of the NHA enzalutamide associated with ADT as an upfront therapy for mHSPC was investigated in two phase III clinical trials. In the double-blind ARCHES trial [13], a total of 1150 patients with mHSPC were 1:1 randomized to receive enzalutamide plus ADT or placebo plus ADT. Previous treatment with docetaxel was allowed. Enzalutamide significantly decreased the risk of radiographic disease progression or death by 61% compared with ADT alone (HR: 0.39, 95%CI: 0.30–0.50, $p < 0.001$), irrespective of previous local and/or systemic treatment, disease volume, and risk [21]. A post hoc analysis demonstrated the clinical advantage of enzalutamide in both cases of de novo mHSPC and metachronous mHSPC [22]. After unblinding, 180 progression-free men assigned to the control arm crossed over to enzalutamide plus ADT. The final prespecified analysis of the OS

(median follow-up 44.6 months) showed that enzalutamide decreased the risk of death by 34% compared with ADT alone (median NR in either group, HR: 0.66, 95%CI: 0.53–0.81, $p < 0.001$) [23].

2.1.4. Apalutamide Plus ADT

The efficacy of the NHA apalutamide plus ADT compared with ADT plus placebo was assessed in the double-blind phase III trial TITAN [14]. Eligible patients had mHSPC with at least one lesion detectable on bone scanning; previous docetaxel therapy was allowed. Among the 1052 enrolled patients, 10.7% had received prior docetaxel chemotherapy and 62.7% had high-volume disease; more than 80% of patients had metastatic synchronous disease. A total of 40% of the patients in the control group crossed over to the experimental arm after the initial unblinding at 22.7 months of follow-up. At a median follow-up of 44 months, apalutamide in combination with ADT significantly decreased the risk of death by 35% compared with ADT alone (mOS: NR vs. 52.2 months, HR: 0.65, 95%CI: 0.53–0.79, $p < 0.0001$) and by 48% after adjusting for crossover. The subgroup analysis pointed out that a benefit from apalutamide was detected in almost all subgroups, notably in both cases of low- and high-volume mHSPC; a trend toward favoring the placebo in men who had received previous chemotherapy was registered, although these patients represented only 10% of the trial population and no interaction between the efficacy of apalutamide and prior docetaxel was detected in a post hoc interaction test [24].

2.2. Triplet Therapy

More recently, the need for further treatment intensification with triplet therapy, consisting of the association of ADT with both docetaxel and NHA, was investigated by the phase III trials ARASENS and PEACE-1. ARASENS [25] enrolled 1306 patients affected by mHSPC that were eligible for ADT and chemotherapy with docetaxel to be treated with either darolutamide or a 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 experimental arm and 42.4 months in the placebo arm, the mOS was NR in the experimental group vs. 48.9 months in the control group.

PEACE-1 [26] was a 2 × 2 factorial design trial that enrolled 1173 patients with de novo mHSPC. Eligible participants were therefore randomly assigned in a 1:1:1:1 manner 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 tumor, SOC plus abiraterone in association with prednisone, or SOC plus abiraterone and EBRT to the primary tumor. To evaluate 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 tumor, they conducted a 2 × 2 factorial analysis. They pooled the groups 2 × 2, distinguishing those who received abiraterone with or without EBRT to the primary tumor into one group and comparing them to those who did not receive it (SOC with or without EBRT to the primary tumor). At a median follow-up of 3.5 years, the addition of abiraterone significantly increased the median rPFS (4.46 vs. 2.22 years, HR: 0.54, 95%CI: 0.41–0.71), with a reduction in the relative risk of radiographic progression by 46%. With a median follow-up of 4.4 years, a significant benefit in terms of the mOS was also reported for 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 being 18% lower than in those who did not receive it. The effect of abiraterone was particularly marked in men with high-volume mHSPC (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 produce a significant increase in neutropenia, febrile neutropenia, fatigue, or neuropathy rates compared with ADT plus docetaxel alone; the only exceptions were hypertension, hypokalemia, and higher levels of aminotransferases, which were more frequently reported in the group treated with abiraterone.

2.3. How to Currently Choose the Most Suitable Treatment for Each Patient

Both ARASENS and PEACE-1 showed that upfront treatment intensification with the combination of ADT, docetaxel, and NHA for de novo mHSPC could become the new SOC since it improved survival outcomes with an acceptable safety profile, especially in patients with high-volume symptomatic disease and without severe comorbidities and a long life expectancy. Probably, the association of the NHA acts as a maintenance treatment, prolonging the effect of chemotherapy. However, no predictive biomarker of response to triplet therapy has been reported up to now.

In patients without a high metastatic burden nor symptomatic disease, considering the lack of robust predictive biomarkers and the different inclusion criteria adopted in each pivotal trial, the choice of the most suitable treatment is currently based mainly on clinical aspects. Abiraterone is known to have pronounced cardiovascular side effects due to the associated increase in mineralocorticoid production [27].

2.4. Oligometastatic Prostate Cancer

Oligometastatic PC (omPC) encompasses a heterogeneous group of tumors characterized by a low metastatic burden [28]. While some works defined omPC based on the number of metastatic lesions, ranging from 3 to 5 lesions, other authors adopted the criteria of low-volume disease according to the CHAARTED trial [8] or low-risk disease according to the LATITUDE trial [10] for the definition of omPC as either de novo or recurrent [29]. Considering that de novo omPC generally displays indolent behavior, with node metastases only or limited bone involvement, and it is associated with a better prognosis compared with men with more than five lesions [30], a benefit from different treatment options may be observed.

Different therapeutic approaches for de novo omPC include locoregional treatments, mainly radiation therapy. In the HORRAD trial [31], 432 patients with primary bone mHSPC were randomized to receive only ADT or ADT in combination with EBRT to the primary tumor; the subgroup analysis demonstrated a trend toward an OS benefit only in men with fewer than five skeletal lesions (HR: 0.68, 95%CI: 0.42–1.10). These promising results were further investigated in the STAMPEDE trial arm H [32]: EBRT to the prostate significantly improved the OS in patients with low metastatic load according to the CHAARTED criteria (HR: 0.68, 95%CI: 0.52–0.90, p = 0.007), reporting an increase in the 3-year survival rate from 73% to 81% with EBRT.

In addition to EBRT to the primary tumor, metastasis-directed therapy (MDT) is a debated issue. MDT is generally used to treat bone metastases or pathological lymph nodes. The only two prospective trials that investigated

stereotactic ablative radiotherapy (SABRT) versus observation, namely, STOMP and ORIOLE, were focused only on metachronous omPC and demonstrated that MDT prolongs the androgen-deprivation-free survival and PFS more than observation alone [33][34].

Adding 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) [35].

3. Genomic Features of mHSPC

3.1. The Role of Liquid Biopsy

Most men with de novo mHSPC will not receive primary surgery; the histologic diagnosis is typically performed on a prostatic biopsy. Therefore, a liquid biopsy could add clinically relevant information in this setting. In a single-center prospective cohort, Vanderkerhove et al. [36] 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 the presence of visceral metastasis. A somatic analysis of ctDNA and tumor tissue revealed a mutational landscape like mCRPC, although without *AR* gene alterations: *TP53* and DDR gene mutations were identified in 47% and 21% of the cases, respectively. The rate of concordance for mutation detection between tumor tissue and ctDNA was 80%, suggesting that de novo mHSPC was a highly clonal disease at diagnosis. On the other hand, in a cohort of 82 Chinese patients with de novo mHSPC, only 50% of men 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 [37][38].

3.2. Prognostic Information

From a prognostic point of view, data regarding the association between the genetic alterations, time to castration resistance, and OS for de novo mHSPC are partial because they were obtained from cohorts including both synchronous and metachronous metastatic disease. Among 424 cases of mHSPC, including 275 men with de novo mHSPC, Stopsack et al. [39] reported a rate of progression to castration resistance that was 1.6-to-5-fold higher in the presence of alterations in *AR*, *TP53*, cell cycle, and MYC pathways and approximately 1.5-fold lower with *SPOP* and Wnt pathway alterations; similarly, the OS rate was 2-to-4-fold higher in the presence of *AR* or cell cycle alterations, and 2-to-3-fold lower if the *SPOP* or Wnt pathway was altered. The sequencing of FFPE tissue from biopsies of 43 patients affected by mHSPC, of whom 30 had de novo disease, revealed a slightly poorer OS with cumulative mutations or alterations in the tumor suppressor genes *TP53*, *PTEN*, and *RB1* [40]; the negative prognostic value of alterations in *TP53*, *PTEN*, and *RB1* was also observed in a cohort of 97 men with mHSPC treated with first-line ADT plus docetaxel or abiraterone acetate, outperforming clinical criteria that predict early disease progression [41]. An association between a shorter OS and alterations in *TP53*, *ATM*, and DDR genes detected on plasma ctDNA was also observed among 53 patients with de novo or metachronous untreated mHSPC [38].

4. Ongoing Phase III Clinical Trials Testing New Therapeutic Approaches for mHSPC

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 tumor microenvironment; this can represent a mechanism of resistance by inducing immune evasion [42]. In the phase Ib Keynote-028 and phase II Keynote-199 trials, mCRPC enzalutamide-refractory patients and previously untreated patients received a combination of pembrolizumab and enzalutamide, reaching potentially improved and durable response rates [43][44]. Based on these premises, the ongoing randomized, double-blind, placebo-controlled phase III KEYNOTE-991 (NCT04191096) [45] is investigating whether this combination therapy for NHA-naive patients with mHSPC is superior to enzalutamide plus placebo. Stratification by prior docetaxel therapy and the presence of high-volume mHSPC 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 the OS and rPFS. Archival or newly obtained tumor 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 for high-volume mHSPC [46].

4.2. Radiopharmaceuticals

Lutetium-177(177Lu)-PSMA-617 is a beta emitter radioisotopic agent that was approved by the FDA in 2022 for the treatment of mCRPC in men who had progressed to an NHA and taxane-based chemotherapy, and whose metastatic lesions express the prostatic-specific membrane antigen (PSMA), as documented via PSMA imaging [47]. Radiopharmaceuticals release alpha or beta radiation to cancer cells via radioisotopes; radiation activates apoptosis via single- and double-strand DNA breaks [48]. PSMAddition (NCT04720157) [49] 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 the SOC (ADT plus NHA) versus SOC alone for 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. The exclusion criterion will be a rapidly progressing tumor that requires chemotherapy. The primary endpoint will be the rPFS. Stratification according to age (≥70 years/<70 years), high-volume vs. low-volume disease, and prior/planned prostatectomy or radiotherapy of the prostate is planned.

4.3. Molecular Target Agents

4.3.1. CDK4/6 Inhibitors

During the G1-S checkpoint, CDK4/6 activation by the AR axis contributes to cancer cell proliferation; among the mechanisms of resistance to NHA, the upregulation of cyclin D1 (whose association with CDK4/6 is crucial for the transition from G1 to S phase) was described [50]. CYCLONE-03 (NCT05288166) [51] is a placebo-controlled phase III study that will randomize about 900 patients affected by high-risk NHA-naïve mHSPC (defined by at least four

bone metastasis and/or visceral disease) to receive either abemaciclib (a selective CDK4/6 inhibitor) or a placebo, plus abiraterone and prednisone. Visceral metastases and de novo mHSPC will be the stratification factors. The primary endpoint will be the rPFS.

4.3.2. PARP Inhibitors

Preclinical and clinical evidence showed that the co-inhibition of the AR axis and PARP generates a combined anti-tumor effect: PARP is involved in the positive co-regulation of AR signaling, and thus, PARP/AR signaling co-inhibition leads to enhanced AR target gene suppression; moreover, treatment with NHAs inhibits the transcription of some DDR genes, inducing synthetic lethality due to cancer cells' inability to repair DNA, even in patients without any DDR alterations [52]. The combination of the PARPi olaparib with abiraterone is FDA- and EMA-approved as a first-line treatment of mCRPC if chemotherapy is not clinically indicated, according to the results of PROPEL [53]. The combination of the PARPis talazoparib and enzalutamide was recently FDA-approved as a first-line treatment for men with homologous recombination repair (HRR) gene-mutated mCRPC, according to TALAPRO-2 [54]. The association of the PARPi niraparib with abiraterone was evaluated both in patients with and without HRR gene-altered mCRPC in the phase III MAGNITUDE trial [55]. Differently from PROPEL, the superiority of the experimental treatment over the control arm (abiraterone plus placebo) was demonstrated only in the cohort with HHR gene-altered mCRPC, while in the HRR proficient cohort, futility was confirmed per the prespecified criteria.

4.3.3. AKT Inhibitors

Inactivation of the tumor suppressor gene *PTEN* via deletion or mutation is frequent in PC, especially in late-stage tumors. PTEN loss of function determines PI3K/AKT signaling pathway activation and suppression of AR transcriptional output. AKTi activates AR signaling, suggesting the potential efficacy of the inhibition of both PI3K and AR signaling pathways [56]. Evidence supporting this association came from the phase III trial IPATential150 [57], which demonstrated that the AKTi ipatasertib, in association with abiraterone, improved the rPFS in patients with mCRPC and PTEN-loss. CAPItello-281 (NCT04493853) [58], which is a randomized double-blind trial, will test the AKTi capivasertib. Approximately 1000 patients with PTEN-deficient mHSPC, as demonstrated using tissue immunohistochemistry (IHC), will be randomized 1:1 to receive capivasertib or a placebo in association with abiraterone. The primary endpoint will be the rPFS.

5. Conclusions

The road toward 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 did not necessarily reflect the biological rationale of the chosen therapy. Transcriptomic profiling of mHSPC 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 regarded as predictive in mCRPC, it remains to be ascertained how these alterations can be exploited in the

mHSPC setting. In this sense, the ProBio (NCT03903835) trial, which is randomizing both mHSPC and mCRPC to receive SOC following national guidelines (control arm) or therapies based on a biomarker signature obtained from diagnostic tissue or liquid biopsy profiling (experimental arm), will probably provide a prospective evaluation of biomarker-driven treatments.

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.
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.
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.
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.
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.
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 2018, 16, 85–89.
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.

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.
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.
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.
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.
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.
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.
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.
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.
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.
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.

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.
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.
21. 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.
22. 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, 102.
23. 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.
24. 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.
25. 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.
26. 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.

27. Cone, E.B.; Reese, S.; Marchese, M.; Nabi, J.; McKay, R.R.; Kilbridge, K.L.; Trinh, Q.D. Cardiovascular toxicities associated with abiraterone compared to enzalutamide-A pharmacovigilance study. EClinicalMedicine 2021, 36, 100887.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. Nabrinsky, E.; Macklis, J.; Bitran, J. A Review of the Abscopal Effect in the Era of Immunotherapy. Cureus 2022, 14, e29620.
36. 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.

37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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, 18, 4079–4087.
46. 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, V352–V353.

47. 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.
48. 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.
49. 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, TPS210.
50. 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.
51. 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 al. 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, S1195–S1196.
52. 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 2022, 14, 801.
53. 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.
54. 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.
55. Chi, K.N.; Rathkopf, D.; Smith, M.R.; Efstathiou, E.; Attard, G.; Olmos, D.; Lee, J.Y.; Small, E.J.; Pereira de Santana Gomes, A.J.; Roubaud, G.; et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J. Clin. Oncol. 2023, 41, 3339–3351.
56. 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.

57. 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.

58. 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.