Factors influencing survival in metastatic castration-resistant prostate cancer therapy

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ABSTRACT

Introduction: The number of patients with metastatic castration-resistant prostate cancer (mCRPC) is expected to increase due to the long life expectancy of those with advanced disease who are also more commonly diagnosed today because of stage migration. Several compounds are available for treating these patients.

Areas covered: We reviewed currently available treatments for mCRPC, their mechanism of action and resistance, and we explored possible predictors of treatment success useful to predict survival in mCRPC patients.

Expert opinion: A combination of molecular, clinical, pathological, and imaging features is necessary to correctly estimate patients’ risk of death. The combination of these biomarkers may allow clinicians to tailor treatments based on cancer history and patients’ features. The search for predictive biomarkers remains an unmet medical need for most patients with mCRPC.

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies in men, representing almost 27% of all tumors in male patients and being the cause of over 10% of all estimated deaths due to cancer [1]. As for other tumors, PCa is a curable disease when localized [2], with estimated survival rates of over 90% at 5 years [2]. However, in the presence of distant metastases, median survival drops to 35 months or less [3]. About 7% of patients with a diagnosis of PCa have metastases at presentation [1]. In addition, in recent decades, an increasing rate of metastatic PCa at diagnosis has been recorded [4].

To date, de novo metastatic and hormone-sensitive metastatic prostate cancer (mHSPC) patients could be treated with a combination of androgen deprivation therapy (ADT) and various compounds from docetaxel to new androgen-receptor-axis-targeted therapies (ARATs), such as darolutamide, apalutamide, abiraterone acetate, and enzalutamide with a meaningful reduction of overall mortality risk [5]. Historically, the use of ADT is well known in the treatment of PCa and is not limited to mPCa [6].

Even if new agents have been introduced, it is likely that almost all patients will develop resistance to castration [7]. Metastatic castration-resistant prostate cancer (mCRPC) is defined by serum castration levels of testosterone in association with PSA serum level increasing (at least three consecutive increase of 50% 1 week apart from each other) or development of new metastatic sites [8].

Due to the long life expectancy of patients with advanced disease, who are also more commonly diagnosed today because of stage migration, an increase in the prevalence of mCRPC is expected. Therefore, several new compounds and strategies have been developed to improve the current treatment landscape. In the last 2 years, several pivotal trials have been published [9–11].

The availability of a huge number of compounds raises important questions including first-line treatment choice, treatment sequencing, and supportive care for mCRPC patients. To the best of our knowledge, the literature lacks a comprehensive review addressing each of these points. We aim to comprehensively review the available literature on mCRPC treatments. We focus on the main predictors of survival in mCRPC patients, with focus on treatment selection. As mechanism of action is key to understanding the development of treatment resistance, we briefly discuss main mechanism of action for currently used drugs.

2. Literature review

We focus on the main aspects of mCRPC treatment and patient features that are associated with survival. Since a growing number of compounds have shown a survival advantage in mCRPC patients, we firstly focused on available compounds and their use. Then, we focused our attention on main predictors of survival reported in prospective and
2.1. Main mechanism of action of currently used treatments

A complex of mechanisms lead to CRPC that could be schematically resumed in increased androgen receptor protein expression that might or might not be associated with mutated androgen receptor expression that could be either natively activated or activated by co-regulatory proteins [12]. Receptor-based acquisition of CRPC phenotype has also been associated with augmented activity or overactivation of proliferative pathways, namely mammalian target of rapamycin (mTOR) and retinoblastoma pathways [12]. This activity is directly associated with gene transcription regulating expression and cell cycle regulatory proteins under control of cyclin-dependent kinase (CDKs), regulatory cyclins, and checkpoint proteins that promotes or inhibits cell cycle allowing the activation of pathways controlling DNA replication and DNA damage responses [12]. While these pathways control the progression of cell cycle to mitoses, the correct functioning of microtubules assembly is responsible for many intracellular processes that lead to cell replication [12]. All these pathways have been targeted by currently available treatments [12].

2.1.1. ARATs

In CRPC, androgen biosynthesis enzymes upregulation has been reported [13,14]. Such an upregulation led to an increase in intra-tumoral androgen concentrations exceeding the levels measured in the blood [13,14]. Moreover, androgen receptors might be overexpressed or mutated, leading to androgen-receptor binding by additional ligands that would not stimulate wild-type receptors [13,14]. Abiraterone acetate and enzalutamide play on this pathway at different levels (Figure 1). Abiraterone inhibits androgen production, while enzalutamide inhibits the activity of androgen receptor.

Enzalutamide is an antiandrogen with a higher binding affinity for androgen receptor if compared to first-generation antiandrogens, such as bicalutamide [15]. Moreover, enzalutamide inhibits nuclear translocation of the androgen receptor and its activity within nucleus [15].

Abiraterone acetate, a pro-drug of abiraterone, is a strong inhibitor of androgen biosynthesis that blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis within testis, adrenal glands, and prostate tumor cells [16]. Phase I studies conducted on human have shown that abiraterone acetate is able to induce testosterone suppression after 1–12 days, which is, however, associated with an increase in luteinizing hormone (LH) levels [16]. Current standard of care is based on the association of abiraterone acetate and LH-RH analogues or antagonists [6]. However, recent phase II trials compared testosterone levels in patients with advanced castration-sensitive PCa treated with standard ADT plus apalutamide, apalutamide alone, and apalutamide plus abiraterone acetate [17]. At 25 weeks, testosterone levels were similar when ADT plus apalutamide or abiraterone plus apalutamide was administered [17]. Instead, testosterone levels increased significantly when only apalutamide was administered [17]. These results suggest that abiraterone acetate alone could achieve similar testosterone suppression to ADT [17]. The main adverse events, linked to the strong inhibition of CYP17, are due to the increases in mineralocorticoids production, which leads to hypokalemia, hypertension, fluid retention, and edema [7]. For this reason, the use of abiraterone is associated with a corticosteroid administration [6].

2.1.2. Docetaxel and cabazitaxel

Docetaxel is a taxane, as paclitaxel, that acts as stabilizing microtubules. Taxanes enhance tubulin polymerization and inhibit its depolymerization [18]. Such inhibition determines cell division failure [18]. Indeed, in the eukaryote’s cells division, chromosome movement, cell secretions, and other fundamental activities depend on microtubules. Its inhibition will exert in cell death (Figure 2) [18]. Docetaxel uptake is higher than paclitaxel, and meantime its efflux from cells is lower, resulting in an higher cytotoxicity in vitro for docetaxel than paclitaxel with lower dosages [18].

Cabazitaxel is a taxane too and was firstly selected due to its activity in taxane-resistant models and its ability to cross the blood–brain barrier [19]. In vitro studies have shown that resistance to taxanes is associated with an alterations in microtubule dynamicity with hypersensitivity to depolymerizing agents and reduced levels of stabilized microtubules [20]. Even if a certain cross-resistance has been highlighted within all taxanes, cabazitaxel showed lower levels of cross-resistance than paclitaxel and docetaxel, justifying its use after progression on docetaxel [6,20]. Main adverse events of taxanes include (febrile) neutropenia, diarrhea, mucositis, alopecia, and nail toxicity [19].

2.1.3. Sipuleucel-T

Sipuleucel-T is an autologous immunotherapy that induces an immune response against the prostatic acid phosphatase [21]. Sipuleucel-T is derived by leukapheresis from autologous peripheral blood [21]. This process leads to mononuclear cells isolation and successive culture with a recombinant fusion protein composed of prostatic acid phosphatase linked to granulocyte-macrophage colony stimulating factor [21]. Such process results in antigen-presenting cell activation, which are infused to the patient. Antitumor activity of the compound
Figure 1. Androgen-receptor-axes-targeted therapies mechanism of action in patients with prostate cancer.
The effects of taxanes on microtubule dynamics

Since tubulin binds to the end of the microtubule in the GTP-bound state, a cap of GTP-bound tubulin is proposed to exist at the tip of the microtubule, protecting it from disassembly.

When hydrolysis catches up to the tip of the microtubule, it begins a rapid depolymerization and shrinkage called catastrophe. The process is followed by rescue.

GTP-bound tubulin can begin adding to the tip of the microtubule again, providing a new cap and protecting the microtubule from shrinking. This process is called rescue.

The classical taxane binding site has been mapped to β-tubulin on the inner lumen of the microtubule.

Signal transduction pathways of taxanes−induced apoptosis

I The BCL-2 family consists of a number of proteins that share BCL-2 homology (BH) domains and control apoptosis by regulating permeabilization of the mitochondrial outer membrane (MOM).

The family is divided into three classes: anti-apoptotic members as BCL2; pro-apoptotic members as BAX and BAD; “BH3 only” proteins that activate other members.

II Taxanes induce BCL-2 and IKKβ2 (an inhibitor receptor) disorganization (step 1) leading to a decrease in pro-apoptotic signals.

III Mitochondrial outer membrane permeabilization (MOMP) leads to the release of pro-apoptotic factors, such as Cytochrome C (step 3) and Smac/DIABLO (step 4).

IV Once Cytochrome C is released, it binds to the cytoplasmic protein AIFM1−1 (Apoptotic Peptide Activating Factor 1), which oligomerizes into a helical structure resembling a wheel (step 5 and 6). The apoplasticase binds and cleaves Proapoptase-9 protein (step 7), releasing its mature, activated form (Caspase 9).

TAXANES

Impact of taxanes on androgen receptor signaling

1 The AR nuclear translocation has been reported to use a microtubule−facilitated pathway. Taxanes might attenuate AR nuclear translocation by destabilizing microtubules.

2 Taxanes induce the nuclear accumulation of FOXO1, a downstream effector of the p53−expressing tumor suppressor that has been shown to inhibit the transcriptional activity of either AR in prostate cancer or constitutively active splice variants of AR at the AR−A2 allele in prostate cancer.

3 Normally, the IAP (Inhibitor of Apoptosis) proteins suppress the activity of a group of caspases preventing the process of apoptosis. PMAC binds and deactivates the IAP proteins (step 8) activating caspase−9 stimulates the subsequent caspase cascade (step 9) that commits the cell to apoptosis (step 10).

Figure 2. Taxanes mechanism of action in patients with prostate cancer.
results from the recruitment and activation of T- and B-cells evoking sustained immune responses against PCa [21]. Most common adverse reactions include chills, fatigue, pain, and low-grade fever [22].

### 2.1.4. PARP inhibitors

Inhibitors of poly(ADP-ribose) polymerase (PARP) are a new antitumor drugs class indicated as an example of precision medicine [23]. PARPs are involved in the repair of single-strand DNA breaks (Figure 3). Otherwise BRCA1 or BRCA2 is involved in double-strand DNA break repair [23]. The proposed model of PARP inhibitors (PARPi) activity is based on the concept that the loss of only one gene is not lethal, but concomitant inactivation leads to cell death. Indeed, PARP1 inhibition alone is not lethal as the DNA could be repaired by other pathways. However, when these other pathways are inefficient, as in the absence of BRCA1/2, the DNA lesions due to PARP inhibition cause cytotoxicity [23]. The activity of PARPi results in the defect of DNA replication fork progression through a not well-understood process that is based on the structural affinity of PARP with nicotinamide [23]. Such structure leads to two main effects: a catalytic inhibition of PARP1 and PARP1 trapping on damaged DNA. How PARP1 is trapped on damaged DNA is not clearly understood and might be due to either the prevention of PARP1 releasing to the inhibition of autoPARylation or by the allosteric changes due to the binding of PARPi to catalytic site. In normally functioning cells, such replication error would be repaired by homologous recombination, thanks to proteins such as BRCA1, BRCA2, PALB2, and RAD51 [23]. However, tumor cells might lack these homologous recombination repair proteins and thus PARP inhibition will result in the use of other reparation strategies by error-prone DNA repair pathways and further fragmentation of the genome that will kill the cells [23].

This model justifies the use of PARPi in several cancer types that share BRCA1/2 deficiency, such as breast, ovarian, and prostate cancer [23]. However, due to the importance of other pathways in DNA damage repair, the use of PARPi, such as olaparib, rucaparib, and talazoparib, has been proposed also in the presence of other mutations [24]. In patients with advanced PCa, up to 30% of patients might present a defect in DNA repair genes [25]. Most important, up to 10% of these defects are germline, thus heritable [26]. Patients with high-risk PCa should be investigated and if germline mutations are found, genetic consulting for other family members is recommended.

#### 2.1.5. PI3K/AKT/mTOR agents

Approximately 40% of early prostate cancer and over 70% of advanced prostate cancer present alterations in PI3K/AKT/mTOR pathway [12]. Most frequently phosphatase and tensin homolog (PTEN) leads to constitutive activation of PI3K pathway, as documented in 60% of CRPC promoting disease progression and poor outcomes in prostate cancer [12]. There is a direct correlation between the PI3K/AKT pathway and androgen signaling [27]. In prostate cancer, androgen receptor signaling inhibition is associated with an increased phosphorylation of AKT, while PTEN loss correlates with decreased androgen receptor activity [27]. Ipatasertib is a competitive ATPase inhibitor of AKT [28] that binds AKT competing with ATP and disrupting its effect on downstream targets [27] (Figure 3). The association of ipatasertib with an inhibitor of androgen signaling pathway can block the glucocorticoid receptor activity and overcome the glucocorticoid receptor-mediated resistance to ARATs therapy [27].

#### 2.1.6. Radium-223

Normal bone integrity is maintained by a balanced cycle of bone resorption and bone formation by osteoclasts and osteoblasts, respectively. Metastatic prostate cancer interacts, via various signaling pathways, with different cellular components in bone microenvironment leading to bidirectional positive feedback leading to characteristic osteoblastic bone metastasis [29]. Radium-223 is an alpha-particle-emitting radionuclide whose deposits were observed in preclinical studies surrounding bone matrix in the vicinity of activated osteoblasts (Figure 4) [29]. A dual mode of action has been identified, consisting of the induction of potentially cytotoxic DNA double-strand breaks leading to tumor cells and osteoblasts and osteoclasts death, disrupting the positive-feedback loops between these cells, suppressing tumor-induced bone pathogenesis [29]. Moreover, an enhanced activity of immune system, by immunosuppression, has been described [29].

#### 2.1.7. Radioligand treatments

\(^{123}\)Iodine is a medium-energy-beta-emitter with a maximum energy of 0.5 MeV and a maximum tissue penetration of <2 mm. The short beta-range of \(^{111}\)In-111 mum provides better irradiation of small tumors [30]. Beta particles are negatively charged electrons whose activity depends on very high radionuclide concentrations within target tissue and its efficacy is based on the position of the decaying atom in respect of target tumor cell, its distance from the tumor cell nucleus, and the radius of the latter [31]. To increase their concentration within target tissue, radionuclides can be labeled to specific proteins. \(^{123}\)Iodine has been conjugated with prostate-specific membrane antigen (PSMA) to concentrate radionuclide in tumor cells (Figure 4). PSMA receptor is known to be expressed on prostate cancer cell and its expression further varies depending on aggressiveness of prostate cancer [30].

### 2.2. Evidence from randomized clinical trials

An overview of the United States Food and Drug Administration approval status and history has been provided in Box 1.

#### 2.2.1. First-line treatments

Currently available first-line treatments for mCRPC include docetaxel, abiraterone acetate, and enzalutamide. Sipuleucel-T, which is considered an option in certain circumstances (asymptomatic or minimally symptomatic patients with no liver metastases, life expectancy >6 months, ECOG performance status 0–1) in the United States, is not available in Europe [32]. The use of ipatasertib is still investigational. Main characteristics of pivotal studies investigating these compounds as first-line treatment are resumed in Table 1.
I. DNA damage and PARPs

DNA single-strand breaks (SSBs) represent the most common type of DNA damage. SSBs are repaired mostly by PARP-dependent Base Excision Repair (BER) pathway.

The Poly (ADP-ribose) Polymerase (PARP) enzyme family is characterized by the ability to catalyze the transfer of ADP-ribose to target proteins.

PARPs are involved in many cellular processes such as DNA repair, genomic stability and programmed cell death.

The main role of some isoforms of PARP family is to detect and initiate an immediate response to DNA SSBs.

Once PARP detects a SSB, it binds to the DNA, undergoes a conformational change, allowing nicotinamide adenine dinucleotide (NAD+), the PARP co-factor, to bind the active site of the enzyme.

PARP then uses the hydrolysis of NAD+ to catalyze the transfer of ADP-ribose moieties on to target proteins.

The synthesis (PARylation) of a Polymeric ADP-Ribose (PAR) chain (1) promotes the recruitment of DNA repair effectors (6) via their PAR-binding domains.

This process leads to the DNA repair (7), which is followed by the degradation of PAR chains via Poly (ADP-ribose) Glycohydrolase (PARG) and the release of PARP and repair enzymes.

Cell death

II. PARP inhibitors

PARP inhibitors (PARPI) promote the catalytic inhibition of PARP-dependent repair (preventing PARylation) and the trapping of PARP on damaged DNA (8).

Failure to repair SSBs can result in OSSBs (Double-Strand Breaks) during DNA replication, so, PARP inhibition can induce further DNA damage (9).

However, DNA damage, can also be repaired through Homologous Recombination (HR) mechanisms.

HR-proficient cells can repair OSSBs originated from SSBs to ensure genome stability and cell survival (10), while HR-deficient cells that cannot repair OSSBs undergo cell death (11).

Cancer cells are frequently mutated in one of their DNA repair pathways. In particular, cancer cells with mutations of BRCA1 and BRCA2 genes, which encode key components of the HR mechanism, are unable to repair OSSBs.

Therefore, PARP inhibitors exploit the principle of synthetic lethality, in which two conditions that independently would not cause cell death applied in combination are lethal.

Figure 3. PARP inhibitors (upper figure) and ipatasertib mechanism of action in patients with prostate cancer.
Radionuclides mechanism of action in patients with prostate cancer.

Bone homeostasis is characterized by a continuous cycle of bone resorption by osteoclasts and bone formation by osteoblasts. Metastatic prostate cancer cells disrupt this balance by interacting with different cellular components of the multiple complex bone microenvironments.

Prostate cancer cells in the bone release growth factors and cytokines, such as BMP, TGF-β, IGFB-1, VEGF, PIGF, and ET-1, which lead to osteoblastic overactivity.

In turn, osteoblasts release growth factors, including VEGF, MCP-1, IL-6, and IL-8, that promote prostate cancer cell growth and survival.

Increased osteoblastic activity also stimulates osteoclastic activity through the secretion of RANKL. Activated osteoclasts release growth factors from the bone and further stimulate tumour growth. Cancer cells, in turn, release growth factors for osteoclasts.

As a result, the tightly regulated crosstalk between osteoclasts and osteoblasts is compromised, leading to an abundance of new disorganized bone (woven bone).

These bidirectional positive-feedback loops between tumor cells and bone resident cells are classically described as a vicious cycle, characteristic of prostate cancer.

Theranostic applications of Lutetium-177

Lutetium-177 Lu is a β-emitter with a half-life of approximately 66 days, so it is able to reach even adjacent cells that may express lower levels of PSMA.

The β-decay of 177Lu β induces a variety of DNA damage, including both single-strand breaks (SSBs) and double-strand breaks (DSBs).

177Lu has a maximal tissue penetration of 2 mm, so it is able to reach even adjacent cells that may express lower levels of PSMA.

In particular, the use of small molecule inhibitors that bind to PSMA more quickly and with higher affinity than whole antibodies, makes this target ideal for radionuclide therapy. Lutetium-177 177Lu is a β-emitter with a PSMA-binding small molecule inhibitor 177Lu-PSMA.

177Lu-PSMA binds rapidly to PSMA and is internalized by endocytosis in the cell, in which it remains over the 67-day half-life of 177Lu.

**Figure 4.** Radionuclides mechanism of action in patients with prostate cancer.
Box1. The United States Food and Drug Administration (FDA) approval history for mCRPC treatment compounds.

| Compound          | Date of approval and therapeutic setting                                                                 |
|-------------------|------------------------------------------------------------------------------------------------------------|
| Abiraterone acetate | FDA initially approved abiraterone acetate with prednisone in 2011 for patients with mCRPC who had received prior chemotherapy, and expanded the indication in 2012 for patients with metastatic CRPC without previous chemotherapy treatment. |
| Enzalutamide      | In 2014, the U.S. Food and Drug Administration approved enzalutamide for the treatment of patients with chemotherapy-naïve mCRPC. Enzalutamide was initially approved in 2012 for use in patients with mCRPC who had previously received docetaxel. |
| Docetaxel         | In 2004, docetaxel, in combination with prednisone, was approved for the treatment of patients with androgen-independent metastatic prostate cancer. |
| Cabazitaxel       | Cabazitaxel was approved in 2010 in those who progress during or after docetaxel treatment. In 2017, cabazitaxel, in combination with prednisone, was approved at lower dosage in the same setting. |
| Sipuleucel-T      | Sipuleucel-T was approved in 2010 for the treatment of patients with asymptomatic or minimally symptomatic mCRPC. |
| Ipatasertib       | Ipatasertib is not approved.                                                                                |
| Rucaparib         | Rucaparib was approved in 2020, by accelerated approval, for patients with deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. |
| Olaparib          | Olaparib was approved in 2020 for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR)-gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. |
| Radium-223        | Radium-223 was approved in 2013, for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. |
| Lutetium-PSMA-617  | Lutetium-Lu 177 was approved in 2022, for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. |

Most historical evidence support the use of docetaxel in mCRPC patients derived from two pivotal trials, namely SWOG 99-16 and TAX 327. Within the SWOG trial, 674 eligible patients were assigned to receive docetaxel and estramustine or mitoxantrone and prednisone. The median overall survival (OS) was 17.5 vs. 15.6 months for patients treated with docetaxel and estramustine compared to the mitoxantrone and prednisone, respectively [33]. Such survival advantage resulted in about 20% reduction in risk of death (HR: 0.80; 95%CI: 0.67–0.97) [33]. Moreover, authors also found a statistically significant longer progression time in the docetaxel and estramustine arm (6.3 vs. 3.2 months) and decline in higher rates of PSA (50 vs 27%) [33]. Higher adverse event rates were recorded in the docetaxel and estramustine arm [33]. These results were corroborated by the TAX 327 trial that showed median survival of 18.9 months for patients treated with docetaxel every 3 weeks compared to 16.5 months of those treated with mitoxantrone. Interestingly, the survival advantage was slightly worse for those receiving docetaxel every week with a median survival of 17.4 months [34]. More recent analyses with extended follow-up also confirmed these results [35].

The use of abiraterone acetate as first-line treatment in mCRPC patients stands on results from COU-AA-302 phase 3 randomized clinical trial [36]. In this study, 1088 asymptomatic or mildly symptomatic patients were randomized to receive either abiraterone acetate plus prednisone or placebo plus prednisone [36]. The median OS was significantly longer for those receiving abiraterone acetate than those receiving placebo (35.3 vs. 30.1 months) with a reduction of the risk of death of about 20% (HR: 0.79; 95%CI: 0.66–0.95) [37]. Most common high-grade adverse events were cardiac disorders and hypertension [36].

Enzalutamide was tested within the PREVAIL trial where 1717 patients were randomly assigned to receive either enzalutamide or placebo [38]. The median OS was 32.4 vs. 30.2 months in the enzalutamide vs. placebo group, respectively [38]. Authors reported a reduction in death risk of about 29% (HR: 0.71; 95%CI: 0.60–0.84) [38]. The most common clinically relevant adverse events were fatigue and hypertension. In the extended analysis, despite the crossover, the survival advantage in patients receiving enzalutamide was confirmed with a median OS of 35.3 vs. 31.3 months [39].

Sipuleucel-T was also tested in a double-blind placebo-controlled phase 3 trial that randomized 512 patients to receive either sipuleucel-T or placebo [40]. A 22% risk of death reduction was recorded in the experimental arm compared to placebo (HR: 0.78, 95%CI: 0.61–0.98) [40]. The median survival was 4.1 month longer in sipuleucel-T group (25.8 vs. 21.7 months) [40]. Main adverse events were chills, fever, and headache [40]. The survival advantage was confirmed in another randomized clinical trials including 127 patients. The median OS was 25.9 vs. 21.4 in Sipuleucel-T vs. placebo arm, respectively [41].

The association of ipatasertib with abiraterone acetate is most recently presented [9]. In the IPAtential150 randomized clinical trial, 1101 patients were randomly assigned to receive ipatasertib plus abiraterone acetate and prednisolone or placebo plus abiraterone and prednisolone [9]. All the included patients had immunochemistry assessment of PTEN status; PTEN loss by immunochemistry was defined as 50% or more of the specimen’s tumor having no detectable PTEN [9]. In the intention-to-treat population, all patients assigned to treatment were included, while in PTEN-loss population, only those with PTEN-loss were included [9]. The median progression-free survival (PFS) was statistically significantly longer in the PTEN-loss group (HR: 0.66; 95%CI: 0.61–0.98; p: 0.038) and reached the prespecified boundary for significance [9]. Conversely, even if a longer PFS was achieved also in the intention-to-treat analysis, it did not reach the prespecified significance [9]. As previously discussed, the use of ipatasertib is still investigational.
| Study          | Intervention          | Comparison                          | Population                        | Main outcomes                                                                 |
|---------------|-----------------------|-------------------------------------|-----------------------------------|-------------------------------------------------------------------------------|
| **Docetaxel** | SWOG 99-16            | Mitoxantrone (day 1)                | 674 patients randomized           | OS: 17.52 vs. 15.6 mo. (p = 0.02, HR: 0.80; 95% CI: 0.67–0.97) PFS: 6.3 vs. 3.2 mo. (p < 0.001) |
|               | Docetaxel (day 2)     | 60 mg/m² every 3 weeks             | 338 patients in the intervention arm |                                                                             |
|               | Estramustine (day 1 to day 5) | 12 mg/m² every 3 weeks           | 336 patients in the control arm    |                                                                             |
|               | Dexamethasone (before docetaxel) | Prednisone                        |                                   |                                                                             |
|               | 60 mg in three doses  | 2 x 5 mg/die                      |                                   |                                                                             |
| **TAX 327**   | Arm A: Docetaxel      | Arm C: Mitoxantrone               | 1006 patients randomized         | OS:                                                                              |
|               | 75 mg/m² every 3 weeks| 12 mg/m² every 3 weeks            | 335 patients in arm A             | Arm A: 18.9 months                                                             |
|               | Prednisone 2 x 5 mg/die| Prednisone                        | 334 patients in arm B             | Arm B: 17.4 months                                                             |
|               | Or                   | 2 x 5 mg/die                      | 337 patients in arm C             | Arm C: 16.5 months                                                             |
|               | Arm B: Docetaxel      |                                     |                                   | Arm A vs. C: HR: 0.76 (95% CI: 0.62–0.94; p = 0.009)                           |
|               | 30 mg/m² weekly      |                                     |                                   | Arm B vs. C: HR: 0.91 (95% CI: 0.75–1.11; p = 0.36)                           |
|               | Prednisone            |                                     |                                   |                                                                               |
| **Androgen-receptor-axes-targeted therapies** | **Placebo**           | Placebo                            | 1088 patients randomized         | OS: 35.3 vs. 30.1                                                             |
| COU-AA-302    | Abiraterone acetate   | 1000 mg/die                        | 546 patients in the intervention arm | Adjusted HR: 0.74 (95% CI: 0.61–0.89; p = 0.0017)                            |
|               |                      | Prednisone                         | 542 patients in the placebo arm   | rPFS: 16.5 vs. 8.2                                                             |
|               |                      |                                    | Inclusion criteria:                | HR: 0.52 (95% CI: 0.45–0.61; p < 0.0001)                                     |
|               |                      | - No previous docetaxel.           |                                   |                                                                               |
|               |                      | - ECOG 0–1.                        |                                   |                                                                               |
|               |                      | - PSA or radiographic progression. |                                   |                                                                               |
|               |                      | - No or mild symptoms.             |                                   |                                                                               |
|               |                      | - No visceral metastases.          |                                   |                                                                               |
| PREVAIL       | Enzalutamide 160 mg/die | Placebo                            | 1717 patients randomized         | OS: 35.3 vs. 31.3 months                                                      |
|               |                      |                                     | 872 patients in the intervention arm | HR: 0.77 (95% CI: 0.67–0.88; p = 0.0002)                                     |
|               |                      |                                     | 845 patients in the placebo arm   | rPFS: 20.0 vs. 5.4 months                                                     |
|               |                      | Inclusion criteria:                |                                   | HR: 0.32 (95% CI: 0.28–0.37; p < 0.0001)                                     |
|               |                      | - No previous docetaxel.           |                                   |                                                                               |
|               |                      | - ECOG 0–1.                        |                                   |                                                                               |
|               |                      | - PSA or radiographic progression. |                                   |                                                                               |
|               |                      | - No or mild symptoms.             |                                   |                                                                               |
|               |                      | - No visceral metastases.          |                                   |                                                                               |
| **Sipuleucel-T** | Impact 2010          | Placebo                            | 512 patients randomized         | OS: 25.8 vs. 21.7 months                                                     |
|               | Sipuleucel-T e.v.     | 341 patients in the intervention arm | 171 patients in the placebo arm | HR: 0.78 (95% CI: 0.61–0.98, p = 0.03)                                      |
|               | every 2 weeks (3 infusions) |                                     | Main characteristics:             |                                                                               |
|               |                      | - Some with previous docetaxel.    | - ECOG 0–1.                       |                                                                               |
|               |                      | - ECOG 0–1.                        | - Asymptomatic or minimally symptomatic. |                                                                               |
|               |                      | - No previous docetaxel.           | - ECOG 0–1.                       |                                                                               |
|               |                      | - ECOG 0–1.                        | - No visceral met.                |                                                                               |
| Small et al.  | Sipuleucel-T         | Placebo                            | 127 patients randomized         | OS: 25.9 vs. 21.4 months                                                     |
|               | Every 2 weeks        |                                     | 82 in the intervention arm        | HR: 1.70; (95% CI: 1.13 vs. 2.56, p = 0.01)                                   |
|               |                      |                                     | 45 in the placebo arm             | rPFS: 11.7 vs. 10.0 weeks (p = 0.052)                                         |
|               |                      |                                     | Main characteristics:             |                                                                               |
|               |                      | - ECOG 0–1.                        | - No corticosteroids.             |                                                                               |

(Continued)
Table 1. (Continued).

| Study | Intervention | Comparison | Population | Main outcomes |
|-------|--------------|------------|------------|---------------|
| **Ipatasertib** | Ipatasertib | 400 mg/die | 1101 patients randomized | PTEN loss population: rPFS: 18.5 vs. 16.5 months; HR: 0.77 (95%CI: 0.61–0.98, p = 0.034 statistically significant at alpha = 0.034) |
|       | Abiraterone  | 1000 mg/die | 547 patients in the intervention arm | ITT analysis: rPFS: 19.2 vs. 16.6 months; HR: 0.84 (95%CI: 0.71–0.99; p = 0.043 not statistically significant at alpha = 0.01) |
|       | Abiraterone  | 1000 mg/die | 554 patients in the placebo arm | |
|       | Prednisolone | 2 × 5 mg/die | Inclusion criteria: Previously untreated for mCRPC, asymptomatic/mildly symptomatic, with and without PTEN loss by IHC | |
|       | Placebo      |            |            |               |

OS: overall survival; rPFS: radiographic progression-free survival; HR: hazard ratio; 95%CI: confidence interval; ITT: intention-to-treat
| Study | Intervention | Comparison | Population | Main outcomes |
|-------|--------------|------------|------------|---------------|
| **Androgen-receptor-axes-targeted therapies** | | | | |
| COU-AA | Abiraterone acetate | Placebo | 1195 patients randomized | OS: 14.8 vs. 10.9 (95% CI: 0.54–0.77; p < 0.001) |
| -301 | Prednisone | | 797 patients in intervention arm | HR: 0.65 (95% CI: 0.54–0.77; p < 0.001) |
| | 2 × 5 mg/die | | 398 patients in placebo arm | PFS: 5.6 vs. 3.6 months (p < 0.001) |
| AFFIRM | Enzalutamide | Placebo | 1199 patients randomized | OS: 18.4 vs. 13.6 months (95% CI: 0.53–0.75; p < 0.001) |
| | 160 mg/die | | 800 patients in enzalutamide arm | HR: 0.63 (95% CI: 0.53–0.75; p < 0.001) |
| | | | 399 patients in placebo arm | rPFS: 8.3 vs. 2.9 months (p < 0.001) |
| **Cabazitaxel** | | | | |
| TROPIC | Cabazitaxel | Mitoxantrone | 755 patients randomized | OS: 15.1 vs. 12.7 months (95% CI: 0.59–0.83; p < 0.0001) |
| | 25 mg/m² every 3 weeks | 12 mg/m² every 3 weeks | 378 patients in cabazitaxel arm | HR: 0.70 (95% CI: 0.59–0.83; p < 0.0001) |
| | Prednisone | Prednisone | 377 patients in mitoxantrone arm | PFS: 2.8 vs. 1.4 months (95% CI: 0.64–0.86; p < 0.0001) |
| | 10 mg/die | 10 mg/die | Inclusion criteria: Previous docetaxel. | HR: 0.74 (95% CI: 0.64–0.86, p < 0.0001) |
| CARD | Cabazitaxel | Abiraterone or enzalutamide based on first-line treatment | 225 patients randomized | OS: 13.6 vs. 11.0 months (95% CI: 0.64–0.89; p = 0.008) |
| | 25 mg/m² every 3 weeks | | 129 patients in experimental arm | HR: 0.64 (95% CI: 0.46–0.89; p = 0.008) |
| | Prednisone | | 26 agents in control arm | rPFS: 8.0 vs. 3.7 months (95% CI: 0.73, p < 0.0001) |
| | 10 mg/die | | | |
| | G-CSF | | | |
| **PARP inhibitors** | | | | |
| PROfound | Olaparib | Enzalutamide or abiraterone based on investigator choice | Cohort A: 242 patients randomized with one alteration in BRCA1/2 or ATM | OS: 18.5 vs. 15.1 months (95% CI: 0.43–0.97; p = 0.02) |
| | 2 × 200 mg/die | | Cohort B: 142 patients randomized with other prespecified genes | HR: 0.64 (95% CI: 0.43–0.97; p = 0.02) |
| | | | | rPFS: 7.4 vs. 3.6 months (95% CI: 0.25–0.47; p < 0.001) |
| | | | | Cohort A + B: |
| | | | | HR: 0.49 (95% CI: 0.38–0.62; p < 0.001) |
| | | | | rPFS: 5.8 vs. 3.5 months |
| | | | | HR: 0.49 (95% CI: 0.38–0.62; p < 0.001) |
| **Radionuclides** | | | | |
| ALSYMPCA | Radium-223 | Placebo | 921 patients randomized | OS: 14.9 vs. 11.3 months (95% CI: 0.58–0.83; p < 0.0001) |
| | 50 kBq/kg every 4 weeks | | 614 patients in experimental arm | HR: 0.70 (95% CI: 0.58–0.83; p < 0.0001) |
| | | | 307 patients in placebo arm | |
| | | | Inclusion criteria: Previous or no previous docetaxel, ECOG 0–2. Two or more symptomatic bone metastases. No visceral metastases. |
| **VISION** | | | | |
| 177Lutetium-PSMA-617 | Standard of care excluding chemotherapy, radioisotopes, or experimental drugs | Standard of care excluding chemotherapy, radioisotopes, or experimental drugs | 831 patients randomized | OS: 15.3 vs. 11.3 months (95% CI: 0.52–0.74; p < 0.0001) |
| | 7.4 GBq every 6 weeks for 4–6 cycles | | 551 patients in experimental arm | HR: 0.62 (95% CI: 0.52–0.74; p < 0.0001) |
| | | | 280 patients in standard-of-care arm | rPFS: 8.7 vs. 3.4 months (95% CI: 0.29–0.57; p < 0.001) |
| | | | | Cohort A: |
| | | | | HR: 0.49 (99.2% CI: 0.29–0.57; p < 0.001) |
| | | | | rPFS: 8.7 vs. 3.4 months |
| | | | | HR: 0.49 (99.2% CI: 0.29–0.57; p < 0.001) |
| **TheraP** | | | | |
| 177Lutetium-PSMA-617 | Cabazitaxel | Standard of care excluding chemotherapy, radioisotopes, or experimental drugs | 200 patients randomized | PSA reduction >50% (ITT): 66% vs. 37%; Difference: 29% (95% CI: 16–42%) |
| | 6.0–8.5 GBq every 6 weeks for 4–6 cycles | | 99 patients in experimental arm | |
| | | | 85 patients in control arm | |

OS: overall survival; rPFS: radiographic progression-free survival; HR: hazard ratio; 95% CI: confidence interval; ITT: intention-to-treat; G-CSF: granulocyte colony-stimulating factor.
2.2.2. Second- and further-line treatments

Currently available second- and further-line treatments for mCRPC already treated with docetaxel include abiraterone acetate, enzalutamide, Radium-223, cabazitaxel, PARP-inhibitor, and radioligand therapy. Immunotherapy with pembrolizumab has also been approved by FDA for all mismatch repair–deficient cancers or in those with unstable microsatellite status (MSI-high), which is, however, a rare condition in prostate cancer [42]. Main characteristics of pivotal studies investigating these compounds as second-line treatment are resumed in Table 2.

Abiraterone acetate has been tested as second-line treatment after docetaxel within the COU-AA-301 clinical trial [43]. Overall, 797 mCRPC patients were randomly assigned to receive abiraterone acetate plus prednisone and 398 to receive placebo plus prednisone [43]. The median survival for the abiraterone group was longer than the placebo (15.8 vs. 11.2 months) with a risk of death reduction of 26% (95% CI: 0.64–0.86) [43].

As for abiraterone acetate, a survival advantage after docetaxel in mCRPC patients has also been proven for enzalutamide [44]. Within the AFFIRM trial, the median OS was longer in patients treated with enzalutamide than placebo (18.4 vs. 13.6 months) with a death risk reduction of about 37% (HR: 0.63; 95% CI: 0.53–0.75) [44].

Cabazitaxel effectiveness as second-line treatment in mCRPC patients has been tested in two pivotal trials, namely TROPIC [45] and CARD [46] clinical trials. Within the TROPIC trial, patients were randomly assigned to receive either prednisone with cabazitaxel or mitoxantrone after evidence of progression during treatment with docetaxel [45]. Overall, 755 men were included in the intention-to-treat analysis [45]. At final analysis, the median OS was longer in the cabazitaxel group compared to mitoxantrone (15.1 vs. 12.7 months) with a risk of death reduction of about 30% (HR: 0.70; 95% CI: 0.64–0.86) [45]. Most common high-grade adverse events were neutropenia and diarrhea that were more common in cabazitaxel group [45]. Within the CARD study, mCRPC patients who received docetaxel and an ARAT (enzalutamide or abiraterone acetate) and experienced a progression were randomly assigned to receive cabazitaxel or the other ARAT (either abiraterone or enzalutamide based on the first-line treatment received) [46]. The median OS was longer in patients treated with cabazitaxel compared to those treated with ARAT (13.6 vs. 11.0 months) with a risk of death reduction of about 36% (HR: 0.64; 95% CI: 0.46–0.89) [46].

Cabazitaxel in combination with carboplatin is suggested by the NCCN Guidelines as an option for fit patients with aggressive-variant mCRPC, defined by the presence of visceral metastases, low PSA and bulky disease, high lactate dehydrogenase (LDH), high carcinoembryonic antigen, lytic bone metastases, neuroendocrine prostate cancer (NEPC) histology, or by unfavorable genomics (defects in at least 2 of TP53, TP3, and RB1) [47]. The addition of carboplatin to cabazitaxel showed longer median PFS compared to cabazitaxel alone in a phase 1–2 trial enrolling patients with mCRPC (median PFS: 4.5 months in the cabazitaxel arm vs. 7.3 months in the cabazitaxel/carboplatin arm; HR: 0.69; 95% CI: 0.50–0.95; p = .018) [48]. Considering the modest improvement in the overall population, subgroup and post-hoc analyses were performed to evaluate whether patients with aggressive variants could derived higher benefit from the addition of carboplatin to cabazitaxel. In a prespecified subgroup analysis, patients with aggressive-variant prostate cancer clinicopathological criteria (AVPC-C) showed a greater benefit from the combination therapy compared to those without AVPC-C. In post-hoc analyses, the presence of aggressive-variant prostate cancer molecular signature (AVPC-MS) assessed by immunohistochemistry (aberrant results for at least two of TP53, RB1, and PTEN) or circulating tumor DNA (ctDNA) (genomic alterations in at least two of TP53, RB1, and PTEN) was associated with benefit in PFS and OS with the addition of carboplatin to cabazitaxel, while there was no advantage for the combination therapy in patients with AVPC-MS-negative tumors [48].

Among radionuclides, radium-223 dichloride has been studied within the ALSYMPCA randomized clinical trial [49]. Overall, 921 patients, not eligible or declined to receive docetaxel, were randomly assigned to radium-223 or placebo [49]. The median OS was significantly longer in those who received radium-223 compared to placebo (14.0 vs. 11.2 months) with a risk of death reduction of about 30% (HR: 0.70; 95% CI: 0.55–0.88) [49].

More recently, radioligand treatments have also been tested. Within the VISION trial [10], the 177Lu-PSMA-617 have been tested in PSMA-positive mCRPC patients previously treated with at least one ARAT and one or two taxane regimen [10]. Patients were randomly assigned to receive 177Lu-PSMA-617 or standard care alone (excluding chemotherapy, immunotherapy, or radium-223) [10]. Those in the experimental arm showed a longer OS (15.3 vs. 11.3 months) with a risk of death reduction of about 38% (HR: 0.62; 95% CI: 0.52–0.74) [10]. Even if adverse events were more frequent in the experimental arm, quality of life was not affected [10]. In a recent phase 2 trial, 177Lu-PSMA-617 have been compared to cabazitaxel, with higher rate of PSA responses in those treated with radioligand (difference 29% in the intention to treat) [50]. Since 177Lu-PSMA-617 showed a survival advantage only in PSMA-positive patients, those who are candidate for treatment with this radioligand should be tested for PSMA expression through PSMA-based imaging.

Within PROfound trial, olaparib efficacy was tested in mCRPC patients who had disease progression while receiving ARATs [11,51]. Patients were eligible if diagnosed with an alteration in prespecified genes with a direct or indirect role in homologous recombination repair. Patients were stratified in two cohorts; cohort A included patients who had at least one alteration in BRCA1, BRCA2, or ATM and cohort B that included patients with any alteration of other prespecified genes [11,51]. Patients were randomly assigned to receive olaparib or physician’s choice of ARAT. A survival advantage in patients treated with olaparib has been recorded in cohort A (HR: 0.69; 95% CI: 0.50–0.97), but not in cohort B (HR: 0.96; 95% CI: 0.63–1.49) [11].

Rucaparib is the second PARPi tested in mCRCP patients with or without measurable disease and with BRCA mutations, within a phase II trial [52]. The primary endpoint was objective
response rate. Results showed 43.5% of objective response rate assessed by a reviewer. Considered these results, rucaparib has been approved provisionally and results from phase III trial are awaited.

2.3. Predictors of survival in mCRPC

2.3.1. Clinical and biochemical factors

Alongside with randomized clinical trials, several studies have been published exploring the efficacy of ARATs in the treatment of mCRPC. Analysis from randomized clinical trials has shown a strong association between performance status, presence of pain, and number of previous lines of treatment and OS [13]. However, baseline patients’ characteristics and outcomes might differ in real-life scenarios when compared to randomized clinical trials [7].

In a retrospective Italian cohort, Cindolo et al. explored predictors of survival in 128 mCRPC patients treated with abiraterone acetate without any previous treatment with docetaxel [53]. Authors showed that treatment was associated with an improvement of self-perceived condition by the patients in 65% of cases, showing that those with higher satisfaction had lower baseline PSA levels, pain, and longer time before developing CRPC [53]. Worse PFS have been reported to be associated with pain, patients satisfaction, baseline PSA levels, and 12-week PSA decline [54]. Similar results have been observed in patients treated with enzalutamide in the same setting. In a retrospective study on 158 Italian patients, baseline PSA >16 ng/ml, the use of opioid for pain control, and previous treatments were all associated with worse PFS [55].

It is well known that prostate cancer mainly affects older patients and whether age could represent a prognostic factor has been the object of investigation in several studies. Analyses from randomized trials in mCRPC confirmed that both taxane chemotherapy and ARATs are efficacious independently of age of patients [56–58]. Chemotherapy administration in older patients could raise more concerns than treatment with ARATs, due to potential frailty of the elderly population and the risk of febrile neutropenia associated with taxanes. However, subgroup analyses of TAX 327 showed that although older men (≥75 years) treated with 3-weekly docetaxel had worse baseline prognostic factors and more often required dose reductions and discontinuation compared to younger men, efficacy and quality of life improvement were comparable in both groups [56]. If these results may also reflect the selected population of patients enrolled in clinical trials, real-life experience also suggested a benefit for docetaxel in patients with good performance status [59], as well as a benefit for enzalutamide or abiraterone in ≥75-year-old patients, notwithstanding the risk of higher toxicity [60]. In conclusion, chronological age should not be considered a priori as a negative prognostic factor in mCRPC, and in men aged >70 years an initial evaluation of health status with the validated G8 screening tool should be performed, in order to evaluate the need of further geriatric assessment and to adapt the treatment to the individual health status of patients [61].

Other researchers highlighted the importance of systemic inflammation. Fan et al. in multivariate Cox regression models showed that high systemic Immune-Inflammation Index level, estimated as platelet X neutrophil/lymphocyte, was a significant predictor of OS and PFS [62].

Bone scan index has been evaluated as an objective tool to assess bone metastasis load among 40 patients treated either with abiraterone or enzalutamide. In multivariable analysis, decreased bone scan index after ARATs was identified as an independent predictor of longer OS [63].

Recently, predictive models to estimate survival in patients treated with abiraterone acetate have been proposed. For instance, Chi et al. proposed a model including six risk factors, namely LDH, ECOG performance status of 2, presence of liver metastases, albumin levels, alkaline phosphatase levels, and time from ADT to abiraterone start [64]. Patients were categorized into three risk groups based on the number of risk factors (0–1 risk factors as good, 2–3 risk factors as intermediate, and 4–6 risk factors as poor). The model showed a fair accuracy (C-index: 0.60) in external validation cohort [64]. The same model was than externally validated by Yang et al. within an independent cohort showing almost identical accuracy (C-index: 0.726) [65]. Another score, the Armstrong nomogram, was developed within the PREVAIL study, including albumin, alkaline phosphatase, LDH, neutrophil-to-lymphocyte ratio, number of bone metastases, pain, pattern of tumor spread, PSA, time to randomization, and treatment type [66]. The continuous individual score was than categorized showing a good accuracy predicting OS and PFS [66]. The nomogram showed a fair accuracy with an incremental AUC of 0.79. The same model was also validated within the COU-AA-302 cohort showing a strong association between the score and OS and PFS [67]. Interestingly, authors also showed a significant interaction between treatment arm and risk group [67]. Patients with low-risk disease had a greater effect from abiraterone treatment than those with intermediate or high-risk disease [67]. A similar model, including pain, performance status, alkaline phosphatase, number of sites of metastatic disease, hemoglobin, PSA, and time since diagnosis, has been developed within TAX327 multicenter study cohort. Results were similar to previously discussed nomograms with a fair accuracy (C-index: 0.70) [68]. A randomized, double-blind, phase 3 study comparing denosumab and zoledronic acid in 1901 men with mCRPC suggested bone-related parameters (alkaline phosphatase ≤143 U/l; bone-specific alkaline phosphatase (BSAP) <146 U/l; corrected urinary N-telopeptide (uNTx) ≤50 nmol/mmol; mild or no pain [Brief Pain Inventory – Short Form score ≤4]; no previous skeletal-related event; longer time from initial diagnosis to first bone metastasis; and longer time from first bone metastasis to randomization) as strong prognostic variables for OS in patients with bone metastases from CRPC [69].

Analyses from TAX 327 focusing on the prognostic impact of the site of visceral metastases showed that patients with liver metastases with or without other metastases had shorter median OS (10.0 mo; 95%CI: 5.4–11.5) than men with lung metastases with or without bone or nodal metastases (median OS: 14.4 mo; 95%CI: 11.5–22.4). Of note, the best median OS
(26.7 mo; 95%CI: 22.3–34.2) was observed in men with lymph-node-only metastases, followed by those with bone-only disease (median OS: 19.0 mo; 95%CI: 18.2–20.7) and bone-plus-node disease (median OS: 15.7 mo; 95%CI: 14.4–17.2) [70]. These results were confirmed by an individual patient data meta-analysis from 8820 men with mCRPC enrolled onto nine phase III trials, which showed that patients with liver metastases had the worst median OS (13.5 months), followed by patients with lung metastases (median OS 19.4 months), while those with nonvisceral bone metastases and node-only disease had a median OS of 21.3 months and 31.6 months, respectively [71].

Taken together, these studies suggest that main predictors of survival in patients treated either with ARATs or docetaxel could be identified from standard patient and tumor evaluation. All the discussed studies reiterate the importance of tumor burden and tumor spread pattern. In addition, objective response to treatment, as documented by imaging or PSA levels drop, represents a strong predictor of survival, as the subjective response in terms of pain and performance status.

The safety profile of therapy also plays a role in treatment decision-making. Hematologic adverse events are a well-known side effect of taxanes. The rates of febrile neutropenia were 3% and 8% in the TAX 327 and TROPIC trial, respectively. In the TAX 327, two (0.3%) treatment-related deaths occurred in the docetaxel group, while in the TROPIC trial, 18 (5%) patients in the cabazitaxel group died within 30 days of the last infusion [35,72]. The most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. The most common non-hematological adverse event related to cabazitaxel was diarrhea (47% all grades), followed by fatigue (37% all grades), which was among the most common non-hematological adverse event in the TAX 327 trial (53% all grades) with alopecia (65%), diarrhea (32%), nail changes (30%), and sensory neuropathy (30%). In PREVAIL and AFFIRM study, adverse events leading to death occurred in 4% and 3% of patients, while in the COU-AA-301 and COU-AA-302, adverse events leading to death were recorded in 13% and 4% of patients, respectively [43,58,66,67]. If the toxicity profile of ARATs appears more manageable compared to that of taxanes, side effects potentially related to abiraterone acetate (i.e. fluid retention/edema, hypokalemia, hypertension, cardiac disorders, atrial fibrillation, and an increase in liver enzymes) or to enzalutamide (i.e. fatigue, diarrhea, hot flashes, musculoskeletal pain, headache, cardiac disorder, seizure) should be considered in order to tailor the treatment choice on the comorbidities and the preference of patients.

2.3.2. Molecular features
Alongside the clinical features, also several molecular biomarkers and liquid biopsy have been evaluated [73]. Aggressivity of mCRPC has been associated with specific molecular features, such as a signature composed of combined defects in at least two of the three tumor suppressors, TP53, RB1, and PTEN, defined as AVPC-MS [74]. As described above, patients with mCRPC and AVPC-MS derived greater benefit with the addition of carboplatin to cabazitaxel compared to AVPC-MS-negative tumors [74].

Antonarakis et al. evaluated the presence of androgen receptor splice variant 7 (AR-V7) mRNA in circulating tumor cells from prospectively enrolled patients with mCRPC who were initiating treatment with enzalutamide or abiraterone [75]. Among those receiving either abiraterone or enzalutamide, those AR-V7-positive had lower PSA response rates and shorter PSA PSA, clinical or radiographic PSA and OS [75]. Such association remained statistically significant even after adjustment considering previous treatments with ARATs, which was associated with increased AR-V7 expression [75]. These findings suggest the use of AR-V7 as possible biomarker of resistance in patients who are candidate to be treated with either abiraterone or enzalutamide [75]. Interestingly, when patients are treated with taxane, similar PSA response has been detected in AR-V7-positive and AR-V7-negative patients. Similarly, PSA PSA and PSA is comparable when AR-V7 positivity is considered. However, in AR-V7-positive patients, clinical outcomes were superior with taxanes compared to enzalutamide or abiraterone therapy [76]. These results were corroborated also when treatment with cabazitaxel only has been considered [77]. Interestingly, AR-V7-positive patients were more frequently pre-treated with abiraterone acetate [77]. The poor response to treatment with abiraterone and enzalutamide in patients with AR-V7 was also confirmed in a prospective multicenter trial. Here, among 118 men with mCRPC, AR-V7 was detected by two different assays that showed high percentage of agreement (>80%). Patients treated with enzalutamide or abiraterone had shorter PFS and OS in the presence of AR-V7, even after adjustment for circulating tumor cells number, and clinical prognostic factors [78].

Liquid biopsy and circulating tumor cells represent a field of great interest in mCRPC. A recent study collected mRNA from circulating tumor cells to measure the expression of androgen receptor variants, androgen receptor targets, and neuroendocrine prostate cancer markers. Hierarchical clustering identified two distinct clusters. Cluster 2 exhibited increased expression of androgen receptor regulated genes and was associated with worse survival [79]. The possibility to integrate circulating tumor cells and cell-free DNA information with radiomic analysis of CT-scan has also been also explored. In 22 patients affected by mCRPC, radiomic analysis identified a signature that strongly correlated with circulating tumor cells count and plasma cell-free DNA levels, suggesting that the integration of cellular, molecular, and radiomic data could be a feasible multi-parametric approach for prediction and disease modeling [80]. Similarly, Conteduca et al. evaluated the possibility to combine plasma tumor DNA and information derived from 18F-fluorocholine PET/CT scan. Authors developed a prognostic score that showed good discrimination in terms of OS and PFS [81]. Circulating cell-free DNA (cfDNA) may represent a useful tool for the monitoring of treatment response, as suggested by the phase II TOPARP-A trial showing an association between decreases in cfDNA concentration and outcome in multivariable analyses [82]. In particular, cfDNA may be particularly helpful in those challenging cases where the PSA level is very low, due to its high sensitivity and
specificity, and it could also allow the detection of resistant clones before clinical or radiographic progression, in order to evaluate early changes to the treatment [83]. However, whether early treatment modification based on cfDNA results may improve outcomes of patients is yet to be demonstrated in clinical trials.

The importance of homologous recombination repair gene has been discussed above. A recent randomized clinical trial showed no survival benefit in patients without mutation of BRCA1/2 treated with olaparib [11]. Unfortunately, tissue-based gene profiling is often unavailable in clinical practice. A recent study investigated the possibility to use circulating DNA when tissue was not sufficient for genetic analyses [84]. Authors reported a 38% increase in the proportion of patients who could be assessed for homologous recombination repair genes status [84]. Analyses from the PROREPAIR-B study, a prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with mCRPC, showed that cause-specific survival (CSS) was halved in germline BRCA2 (gBRCA2) carriers (17.4 vs. 33.2 months; p = .027), and gBRCA2 mutations were identified as an independent prognostic factor for CSS (HR: 2.11; p = .033) [85]. Moreover, a significant interaction between gBRCA2 status and treatment type (ARATs vss taxane therapy) was observed, and clinical outcomes were improved in gBRCA2 carriers treated in first line with abiraterone or enzalutamide compared with taxanes. These results suggest that gBRCA2 mutations could represent an independent prognostic factor for survival in mCRPC and that the initial treatment choice may impact on the clinical outcomes of patients with gBRCA2 [85]. However, a recent study conducted on 190 men with mCRPC failed to show a consistent survival advantage based on DNA damage repair defects when patients were treated with cabazitaxel [86]. Interestingly, it has also been suggested that patients harboring DNA repair gene aberrations could have a higher likelihood of response to carboplatin-based chemotherapy than those without DNA repair gene alterations [87,88]. Unfortunately, a direct comparison between carboplatin and olaparib in mCRPC is lacking.

PTEN loss, which occurs in approximately 40–50% of patients with mCRPC, activates AKT signaling, enhancing cell proliferation and tumor progression, and leading to worse outcomes and reduced benefit from androgen-receptor pathway blockade [89]. As discussed before, the addition of ipatasertib, a competitive ATPase inhibitor of AKT, to abiraterone acetate showed a longer PFS compared to abiraterone acetate alone in the subgroup of patients with PTEN loss included in the ipATential150 trial, suggesting PTEN loss as a potential predictive factor of response to AKT inhibition [9].

2.3.3. Surrogate endpoints of overall survival
Considering the increasing live expectancy of patients with mCRPC, recent research investigated intermediate or surrogate end points short of OS, in order to expedite trial conduct and support regulatory approval of effective drugs. Using two different statistical methods in PREVAIL trial, Prostate Cancer Clinical Trials Working Group 2 (PCWG2) definition of radiographic PFS (rPFS) and OS was found to be positively correlated [90]. Of note, the definition of PFS proposed by PCWG2 was based on a ‘2 + 2’ rule, with progression declared when at least two new lesions were seen on the first on-treatment scan, followed by at least two additional lesions on the second posttreatment scan, in order to control for tumor flare suggestive for bone healing and avoid unnecessary early change of therapy. A recent meta-analysis by Halabi et al. [91] demonstrated moderate correlation between treatment effects of rPFS and OS in patients with mCRPC. However, rPFS did not meet the pre-specified trial level surrogacy threshold of 0.7. On the contrary, recent evidence based on individual patient data from randomized trials in mHSPC suggested that both rPFS and clinical PFS appear to be valid surrogate endpoints for OS [91]. Therefore, the search of reliable surrogate end points still represents an unmet clinical need in mCRPC.

2.3.4. Impact of treatment intensification in mHSPC and novel imaging in mCRPC
After recent advances in mHSPC, intensification of systemic treatment with ARATs and/or docetaxel in addition to ADT should be considered the mainstay of treatment for most patients with mHSPC. However, the impact of the early administration of treatments on outcomes of mCRPC is yet to be elucidated, as well as the impact on tumor biology of long ARATs administration in mHSPC.

Another point uncertainty regards the impact on mCRPC outcomes of novel imaging such as PSMA-PET, potentially detecting disease not otherwise evident with conventional imaging and leading to anticipation of treatment or early treatment changes, even if not supported from high level evidence to date. Interestingly, previous evidence showed the potential prognostic value of tracer uptake (SUV) cutoff values on 68 Ga-PSMA PET/CT in patients with advanced prostate cancer [92].

A recent study in 56 men with mCRPC treated with up to six doses of 177LuPSMA-617 and a radiation sensitizer (NOX66) suggested change in quantitative PSMA-total tumor volume as a potential prognostic biomarker with 177LuPSMA-617 therapy, independent of FDG-PET parameters, PSA, or radiographic progression [93]. Moreover, updated analyses from the TheraP trial suggested that PSMA SUVmean ≥10 was predictive of a higher likelihood of response to LuPSMA than cabazitaxel, while a high volume of disease on FDG PET was a negative prognostic factor regardless of the treatment [94].

2.4. Sequencing treatments strategies
A recent large analysis of treatment sequences in Europe and Japan highlighted that the most common first-line therapy is based on ARATs, while taxanes (especially docetaxel) are more frequently used as second-line treatment [95]. So, the most frequently used sequence are ARATs followed by taxanes, the second-most frequently used sequence if based on taxanes followed by ARATs [95]. Such sequencing strategy is justified by currently available evidence on the topic. Recent retrospective analysis has shown little or no survival benefit based on sequencing in ‘real world’ [96], confirming the

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number of treatment lines still mirrors the treatment success [55], which is likely related to the lack of validate predictive biomarkers of response.

Fan et al. relied on a cohort of 104 patients diagnosed with mCRPC to test the effect of sequential treatment using docetaxel and abiraterone vs. abiraterone followed by docetaxel [62]. Authors failed to find any statistically significant difference in terms of OS or PFS according to different sequencing strategies [62]. Considering the results from CARD randomized clinical trial, the sequencing of two ARAts should be avoided, while a taxane should be preferred [46].

Results from PROfound randomized clinical trial support the sequence of ARAts to PARPi in the presence of specific alteration of homologous recombination repair genes [11,51]. Aldea et al. evaluated 190 mCRPC patients treated with cabazitaxel. Patients were stratified according to the presence or absence of DNA damage repair defects. In a subgroup analysis, no PSA response was observed after cabazitaxel in patients previously treated with PARPi [86].

The randomized phase 2 TheraP trial showed higher PSA response, PFS, and fewer grade 3 or 4 adverse events in mCRPC patients treated with \( ^{177} \text{Lu} \)Lu-PSMA-617 compared to cabazitaxel [50]. However, the recent update of the trial reported similar OS, a secondary endpoint, for the two treatment arms [94]. If from one side, considering the similar OS and the significant improvements in PSA response and PFS, as well as the favorable safety profile, these results may support the choice of \( ^{177} \text{Lu} \)Lu-PSMA-617 over cabazitaxel for patients with PSMA-positive mCRPC, progressing after docetaxel and ARAts, from the other side, there is no level 1 evidence based on OS data to support such treatment sequencing.

3. Expert opinion

mCRPC is a lethal tumor with no available treatment able to cure the disease. However, research has led to the development and commercialization of a tremendous amount of treatments for mCRPC that are able to prolong survival and improve quality of life [6,53]. To date, several biomarkers have been evaluated [73], including circulating biomarkers, liquid biopsy, and specific gene signatures [73,79]. Some of these biomarkers need to be investigated before starting specific treatments as discussed above, as for the presence of BRCA1/2 mutations before olaparib treatment [51] or the expression of PSMA by PET PSMA before starting treatments with radionuclide [10]. However, in the near future, a tailored treatment based on specific biomarker signature would be desirable. The effectiveness of this approach will be evaluated in the Prostate Biomarkers (ProBio) study (NCT03903835) [97]. The ProBio trial is an outcome-adaptive, multiarm, open-label, multiple-assignment randomized, biomarker-driven platform trial that will evaluate the efficacy of treatments and treatment sequencing based on a physician’s standard-of-care preference vs. biomarker-signature-based treatments in mHSPC and mCRPC [97]. Such trials will provide fundamental information that could finally answer unmet needs.

Accurate assessment of prognosis by using tools potentially combining clinical and molecular characteristics could help clinicians in decision-making, which is becoming more and more complicated with the increasing number of available drugs. Tools aimed at the assessment not only of prognostic but also of predictive factors could also guide intensification or even deintensification of treatment with the aim of a personalized treatment approach.

In the absence of level 1 evidence, physicians should always rely on patients’ history and characteristics to tailor their treatment. For instance, patients already treated with ARAts might not have a benefit with a second line of ARAts, as shown in CARD trial [46]. Such resistance could be related to androgen receptor variants, as have been previously described [78]; thus, in these patients, a taxane should be used, since its effect is not affected by the presence of androgen receptor variants [76,77]. On the other hand, not all patients might be eligible for treatments with taxane. In these cases, genetic profiling, looking for specific mutations, such as those of BRCA genes, should be performed. Indeed, in some patients, the use of PARPi would be a preferable choice [51].

To date, even without evidence from randomized clinical trials, we know enough about mCRPC tumor biology and about mechanism of resistance for each drug to guide treatment choice. Still, our efforts should continue in the field of molecular biology to further expand our knowledge. The landscape of mCRPC is rapidly changing and more evidence are available with the treatment of this tumor that appears to be more and more multidisciplinary.

4. Conclusion

Today several treatments are available for mCRPC. The main predictors of survival are a number of treatment lines, cross-resistance between different drugs, and presence of specific genomic features, such as alteration in DNA repair genes. Currently available nomograms showed fair accuracy in predicting survival in mCRPC patients and take into account several laboratory markers and patient characteristics.

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