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Management of systemic prostate cancer: current algorithm from castration sensitive to castration resistant setting

C. D'ANIELLO[1], C. CAVALIERE[2], C. FOGLIA[1], S. FACCHINI[3], F. URICCHIO[4], R. BALSAMO[4], E. FRANZESE[5], S. DE FALCO[5], M. IZZO[5], M. LATERZA[5], C. LIGUORI[5], P. COPPOLA[5], Y. DIESSA[5], M. FASANO[3], G. DI LAURO[6], S. LAI[6], V. COCETTA[7], S. PISCONTI[8], V. MONTESARCHIO[1], G. FACCHINI[5]

[1]Division of Medical Oncology, AORN dei Colli Ospedali Monaldi-Cotugno-CTO, Naples, Italy
[2]Medical Oncology Complex Unit, ASL NA3 Sud "Ospedali Riuniti Area Nolana", Nuovo Gragnano Hospital, Gragnano (NA), Italy
[3]Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Naples, Campania, Italy
[4]Division of Urology, AORN dei Colli Ospedali Monaldi-Cotugno-CTO, Naples, Italy
[5]Medical Oncology Complex Unit, ASL Napoli 2 Nord 'Santa Maria delle Grazie' Hospital, Pozzuoli (NA), Italy
[6]Division of Urology, ASL Napoli 2 Nord 'Santa Maria delle Grazie' Hospital, Pozzuoli (NA), Italy
[7]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padua, Italy
[8]Medical Oncology Department, San Giuseppe Moscati Hospital, Taranto, Italy

Abstract. – In recent years, the advanced knowledge of clinical, biological and molecular features of prostate cancer have led to the introduction of new drugs and have allowed the relocation of old drugs in different settings. In this way, the new concepts of systemic disease arise: high risk or high volume vs. low risk and low volume disease castration sensitive prostate cancer (CSPC), diversifying the use of previously approved drugs (CRPC) and opening new scenarios for sequence therapy. The aim of this review is to integrate new developments into the medical management of systemic prostate cancer.

Key Words:
Castration resistant prostate cancer, Castration sensitive prostate cancer, New management of systemic prostate cancer, Prostate cancer.

Introduction

Prostate cancer (Pca) is the leading cause of cancer death in men, and it is currently the most frequent malignancy among males and accounts for over 20% of all cancers diagnosed over 50 years old[1-3]. The management of local or loco-regional disease include curative options, such as radical prostatectomy (RP), external beam radiotherapy (RP) and low-dose-rate brachytherapy with or without androgen deprivation therapy (ADT). Until last years, systemic Pca, including only biochemical recurrence, systemic recurrence after local treatment, or systemic disease at onset, benefited from endocrine therapy named "castration" or "androgen deprivation therapy" (ADT). Nevertheless, after a variable period (generally 1-3 years), the tumor progresses despite ADT and becomes castration resistant (CRPC), namely refractory to a conventional ADT, and suitable for other treatments, such as chemotherapy, docetaxel or cabazitaxel, or next generation androgen receptor inhibitors (NGARi), abiraterone or enzalutamide, with a median overall survival of 20-30 months[4-9]. In recent years, the advances in knowledge of the clinical, biological and molecular features of prostate cancer have led to the introduction of new drugs. The introduction of new therapies, have allowed the relocation of old drugs in different settings, introducing a new concept of systemic disease: high risk or high volume *vs.* low risk and low volume disease castration sensitive prostate cancer (CSPC), diversifying the use of previously approved drugs (CRPC) and opening new scenarios for sequence therapy.

Corresponding Author: Carla Cavaliere, MD; e-mail: carla.cavaliere@hotmail.it

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Post Local Curative Treatment Recurrence

Biochemical Only Recurrence After Local Treatment

This setting includes different clinical conditions: biochemical recurrence after radical prostatectomy (RP) or post-irradiation too; in any case a radiological reassessment is necessary to exclude systemic disease. Conventional staging (Total body Computed Tomography and Bone Scan) replaced by the PSMA-PET imaging, based on its superior sensitivity and specificity. Papa et al[10] performed a systematic review and meta-analysis to update reported predictors of positive 68Ga-PSMA PET. They confirmed the role of Ga-68-PSMA PET to improve detection of metastases with biochemical recurrence, particularly at low pre-PET PSA levels of >0.2 ng/ml (33%) and 0.2-0.5 ng/ml (45%). PET PSMA staging is able to differentiate real biochemical recurrence (cM0) from systemic disease (cM1).

Biochemical Only Recurrence After Radical Prostatectomy

This setting includes patients with PSA above the value of 0.2 ng/mL and with at least two subsequent determinations with increasing values, after radical prostatectomy. Several retrospective studies[11-15] confirm the role of Salvage Radiotherapy (SRT) with a significant increase in prostate cancer-specific survival. This advantage seems to be higher in the PSADT less than 6 months subgroup, although other studies[11-13] confirm this advantage regardless PSA-DT and other prognostic features such as pathological stage or Gleason score; however, in good prognosis patients (Gleason score $\leq$ 6, PSA-DT > 10 months) a wait-and-see strategy may be a viable option[14,15]. The role of hormone therapy (HT) combined with SRT is still unknown. Pre-SRT PSA $\geq$ 1.0 ng/mL, pathological stage $\geq$ T3a, Gleason score $\geq$ 7, PSADT < 12 months (particularly < 3 months) represent poor prognostic factors, suggestive of SRT failure, and therefore, combination therapy could be an option[16-19]. Several randomized studies have shown conflicting results with the addition of ADT to SRT in terms of OS, particularly in patients with unfavorable-risk prostate cancer. The GETUG-AFU 16 trial confirms the efficacy of short-term ADT (6 months-LHRH) plus SRT, reducing the risk of biochemical or clinical progression (80% [95% CI 75-84] *vs.* 62% HR, 0.50; 95% CI, 0.38-0.66; p<0.0001), without advantage in terms of OS (HR, 0.7; 95% CI, 0.4-1.2, p=0·18)[20,21]. 9601 Studies[22,23] on RTOG showed a significant increase in OS for patients treated with long-term ADT (2 years-bicalutamide) plus SRT (HR, 0.75; 95% CI, 0.58-0.98, p=0.04). Definitely, only patients with unfavorable-risk would seem to benefit from the use of ADT in addition to SRT; conversely, the potential side effects of ADT spared in patients with favorable pathological features[24,25].

Biochemical Only Recurrence After Irradiation

This setting includes patients undergoing RT with or without ADT as local treatment with a POST-RT PSA values that exceed the lowest "nadir" above the value of 2 ng/ml. Patients with favorable risk (clinical stage < T3a Gleason score $\leq$ 6, PSA-DT > 10 months) consider alternative local approach (re-irradiation, rescue prostatectomy, HIFU, cryotherapy) or observation, conversely use a systemic treatment (ADT) for unfavorable risk patients (clinical stage $\geq$ T3a, Gleason score $\geq$ 7, PSADT < 12 months)[26,27]. In unfavorable group, immediate ADT significantly improve OS compared with delayed strategy, reaching a 5-year OS of 86·4% (95% CI, 78.5-91.5) in the delayed *vs.* 91.2% (95% CI 84.2-95.2) in the immediate arm (log-rank p=0.047)[28]. Intermittent schedule is non-inferior to a continuous administration and seems to offer a better quality of life and lower side effects[29].

Non-Metastatic Castration-Resistant Prostate Cancer (CRPC-M0)

This setting includes patients with only biochemical progression (increase of PSA) without local or distant recurrence, during ADT treatment[30]. Based on currently available evidence, abstention from further therapeutic options may be considered in patients with long PSA-DT (> 10 months); alternatively, additional ADT manipulations (e.g., flutamide, bicalutamide) should be reserved for those at highest risk of disease progression, defined mainly by a short PSA DT ($\leq$ 10 months) or a high initial Gleason score (>7), with a long-life expectancy[31]. Recently, three clinical trials[32-34] evaluated the role of next generation

androgen receptor inhibitors (NGARi) (apalutamide-enzalutamide-darolutamide) and whose results have changed the clinical management of high-risk CRPC-M0 (Table I).

Apalutamide

A phase 3 SPARTAN trial evaluated apalutamide at a dose of 240 mg daily plus ADT *vs.* placebo plus ADT in CRPC-M0 with a PSA-DT ≤ 10 months and PSA > 2 ng/ml. The median metastasis-free survival was 40.5 months in the apalutamide arm *vs.* 16.2 months in the placebo group (HR for metastasis or death, 0.28; 95% CI, 0.23 to 0.35; $p<0.001$), with a median OS of 73.9 *vs.* 59.9 months, (HR, 0.78; 95% CI, 0.64-0.96; $p=0.016$). The time to symptomatic progression was significantly longer with apalutamide than with placebo (HR, 0.45; 95% CI, 0.32 to 0.63; $p<0.001$[32,35,36].

Enzalutamide

A phase 3 PROSPER trial evaluated enzalutamide at standard dose of 160 mg daily plus ADT *vs.* placebo plus ASR in CRPC-MO with a PSA-DT ≤ 10 months and PSA > 2 ng/ml. The median metastasis-free survival was 36.6 months in the enzalutamide group *vs.* 14.7 months in the placebo arm (HR for metastasis or death, 0.29; 95% CI, 0.24 to 0.35; $p<0.001$), with a median OS of 67.0 *vs.* 56.3 months (HR, 0.73; 95% CI, 0.61 to 0.89; $p=0.001$)[33,37].

Darolutamide

A phase 3 ARAMIS trial evaluated darolutamide at dose of 600 mg BID plus ADT *vs.* placebo plus ADT in CRPC-MO with a PSA-DT ≤ 10 months and PSA > 2 ng/ml. The median metastasis-free survival was 40.4 months with darolutamide *vs.* 18.4 months with placebo (HR for metastasis or death, 0.41; 95% CI, 0.34 to 0.50; $p<0.001$). The overall survival at 3 years was 83% (95% CI, 80 to 86) in the darolutamide group and 77% (95% CI, 72 to 81) in the placebo arm. The risk of death was significantly lower – by 31% – in the darolutamide group than in the placebo group (HR, 0.69; 95% CI, 0.53 to 0.88; $p = 0.003$). Darolutamide was also associated with a significant benefit in all other secondary endpoints, including the time to first symptomatic skeletal event and the time to first use of cytotoxic chemotherapy[34,38].

CRPC-M0 Treatment Debate

Kumar et al[39] performed a network meta-analysis to provide an indirect comparison of oncologic outcomes and adverse events (AEs). MFS was significantly lower in patients receiving darolutamide *vs.* both apalutamide (HR, 0.73, 95% CI, 0.55-0.97) and enzalutamide (HR, 0.71; 95% CI, 0.54-0.93). In terms of PFS, apalutamide showed a slightly higher rate compared to darolutamide (HR, 0.76; 95% CI, 0.59-0.99). There was no statistically significant difference in terms of OS and AEs profile. Conversely, a Bayesian analysis showed that apalutamide and enzalutamide had a 56% and 44% likelihood of maximizing MFS, respectively, regardless of PSA doubling time and PS. There was a 44%, 41%, and 15% probability that apalutamide, darolutamide and enzalutamide offered the greatest OS benefit, respectively. Apalutamide and enzalutamide may result in improved oncologic outcomes. Darolutamide may result in fewer AEs[40]. Overall, there were no differences in MFS HR after matching in either comparison. However, the different safety profile could impact the clinical decision-making: fall, fracture, and rash rates were statistically significantly lower in darolutamide treatment versus apalutamide, as well as fall, dizziness, mental impairment and fatigue were statistically significant lower in darolutamide arm *vs.* enzalutamide[41-44]. To date, a direct comparative data is not available to guide treatment decision, so in our judgment apalutamide, enzalutamide and darolutamide are significantly more effective than placebo, but apalutamide and enzalutamide offer the best reduction in risk of metastases or death (72% and 71%, respectively *vs.* 59% with darolutamide), while darolutamide appears to have the most favorable tolerability profile.

Table I. Reported RCTs in CRPC-M0.

Trial	Agents	N	HR for MFS	MFS (mon)	HR for OS	OS (mon/%)
AR inhibitors						
§Spartan[32]	ADT + APA	1207	0.28	40.5	0.78	73.9
§Prosper[36]	ADT + ENZA	1401	0.29	36.6	0.73	67.0
§Aramis[37]	ADT + DAR	1509	0.41	40.4	0.69	83% at 3 yrs

Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

This heterogeneous group includes both de novo mCSPC patients and those presenting with systemic recurrence after local treatment failure.

ADT

Until recently, castration condition obtained with bilateral orchiectomy, or LHRH agonist or antagonist, or an LHRH agonist plus a first-generation antiandrogen (TAB), has been the gold standard treatment of mCSPC[45,46]. The use of the LHRH antagonist may represents the first treatment choice, according to the clinical benefits, including a significant improvement in PFS and OS, as well as reduced incidence of joint, musculoskeletal, and urinary tract adverse events, compared with LHRH agonists[47]. Recently, a new generation orally LHRH agonist, relugolix achieved rapid, sustained and superior suppression of testosterone levels compared to LHRH agonist, with a lower incidence of major adverse events (HR 0.46; 95% CI, 0.24 to 0.88)[48]. Generally, considering the higher incidence of side effects (hot flashes, loss of potency and libido, fatigue, reduction of muscle mass, osteoporosis, anemia), especially, the increase incidence of metabolic syndrome, the optimization in terms of timing (early versus delayed) and duration (intermittent versus continuous) of ADT represents a research interest[49]. Several randomized trials[50-52] have evaluated this issue with conflicting results on OS benefit. Sciarra et al[52] conducted a review analysis of 7 phase 3 trials randomizing 4675 patients to intermittent ADT (IAD) *vs.* continuous ADT (CAD). In terms of OS, the HR for IAD and CAD was very similar (range: 0.98-1.08). The QoL using IAD was modest. Although in patients with biochemical recurrence, IAD is comparable to CAD, in the metastatic setting prolonged, ADT continues to be the standard of care. Generally, therapy should be tailored to patient's individual needs, including a close balance between side effects and any comorbidities. Nowadays, the advanced knowledge of the clinical, biological and molecular feature of prostate cancer led to the introduction of new drugs, different treatment strategies also with old drugs but in different settings. A new concept of systemic disease was born: high risk or high volume versus low risk and low volume disease hormone sensitive prostate cancer (HSPC), diversifying the use of previously approved drugs (CRPC) and opening new scenarios for sequence therapy[53] (Tables II, III).

High Risk Metastatic Castration Sensitive Prostate Cancer (HR-mCSPC)

HR-mCSPC patients defined according to LATITUTE criteria: at least two of the three following criteria – Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastases except lymph node metastases.

Abiraterone

The phase 3 LATITUDE trial enrolled 1199 high-risk mCSPC patients to ADT plus Abiraterone at standard dose *vs.* ADT plus dual placebos. After a follow-up of 51.8 months the

Table II. Low-volume/low-risk disease mCSPC.

Trial	Comparator arm	N	HR for PFS (or other endpoint)	HR for OS
Docetaxel				
§Chaarted[61]	ADT + DOC	277	0.70 (time to CRPC)	1.04
§Getug-15[59]	ADT + DOC	202	NA	1.02
§Stampede-doc[64]	ADT + DOC	124	NA	0.76
AR inhibitors				
§Latitude[55]	ADT + ABI	243	NA	0.72
§Stampede-abi[56]	ADT + ABI	428	0.24 (FFS)	0.66
§Enzamet[66]	ADT + ENZA (± DOC)	537	0.30	0.43
§Arches[67]	ADT + ENZA*	423	0.25 (rFFS)	TBD
§Titan[65]	ADT + APA*	392	0.36	0.67
RT				
§Stampede arm H[84]	ADT + RT to prostate	819	NA	0.68
§Horrad[83]	ADT + RT to prostate	160	NA	0.68

*Prior docetaxel allowed.

Table III. High-volume/high-risk disease mCSPC.

Trial	Agents	N	HR for PFS (or other endpoint)	HR for OS
Docetaxel				
§Chaarted[61]	ADT + DOC	513	0.58 (time to CRPC)	0.63
§Getug-15[59]	ADT + DOC	183	NA	0.78
§Stampede-DOC[64]	ADT + DOC	148	NA	0.81
AR inhibitors				
§Latitude[55]	ADT + ABI	955	NA	0.62
§Stampede-ABI[56]	ADT + ABI	473	0.31 (FFS)	0.54
§Enzamet[66]	ADT + ENZA (± DOC)	588	0.45	0.80
§Arches[67]	ADT + ENZA*	727	0.43 (rPFS)	TBD
§Titan[65]	ADT + APA*	660	0.53	0.67
RT				
§Stampede-RT[84]	ADT + RT to prostate	1120	NA	1.07
§Horrad[83]	ADT + RT to prostate	272	NA	1.06

*Prior docetaxel allowed.

median OS was significantly longer in the abiraterone group (53.3 *v*s. 36.5 months) (HR, 0.66; 95% CI, 0.56 to 0.78; $p<0.001$). The median radiographic PFS was 33.0 months in the abiraterone group and 14.8 months in the placebo group (HR for disease progression or death, 0.47; 95% CI, 0.39 to 0.55; $p<0.001$). All secondary endpoints were achieved, including longer time until pain progression or next subsequent therapy for prostate cancer or initiation of chemotherapy ($p<0.001$). The most common treatment-related serious adverse event was hypokalemia (1%)[54,55]. The STAMPEDE-ABIRATERONE trial evaluated the efficacy of abiraterone in M0 (2 of 3 high risk factors: stage T3/T4, PSA>40 ng/ml, Gleason Score=8-10 or N1) or M1 (all categories), with a 71% relative improvement in the time to treatment failure, which translated into a 37% difference in OS compared to ADT alone[56]. A post-hoc subgroup analysis of the STAMPEDE-ABIRATERONE trial including only M1 mCSPC patients, evaluated abiraterone in low (48%) *vs.* high-risk (52%) patients, according to the LATITUDE criteria. In the low-risk subgroup, the combination of abiraterone plus ADT showed a survival advantage (HR, 0.66; 95% CI, 0.44-0.98): the absolute 3-yr survival was 83% with ADT + abiraterone and 78% with ADT alone. The same advantage demonstrated in in the high-risk disease subgroup (HR, 0.54; 95% CI, 0.41-0.70): the absolute 3-years survival was 65% with ADT + abiraterone and 45% with ADT alone. The combination treatment reached all the secondary endpoints in both risk groups[57].

High Volume Metastatic Castration Sensitive Prostate Cancer (HV-mCSPC)

HV-mCSPC patients defined according to CHAARTED criteria: visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis.

Docetaxel

The phase III GETUG-AFU15 enrolled 192 patients with mCSPC to docetaxel at standard dose plus ADT *vs.* ADT alone. At median follow-up of 50 months, the median OS was 58.9 (95% CI, 50.8-69.1) in the docetaxel group *vs.* 54.2 months (42.2-not reached) in the ADT alone arm (HR, 1.01; 95% CI, 0.75-1.36)[58]. The post-hoc analysis, stratifying patients in high versus low-volume disease according to CHAARTED criteria, demonstrated a non-significant 20% reduction in the risk of death in the HV disease [mOS, 39.8 (95% CI, 28.0-53.4)] *vs.* 35.1 months (95% CI, 29.9-43.6) (HR, 0.78; 95% CI, 0.56-1.09; $p=0.14$)]. No OS improvement in LV group [mOS, not reached; 95% CI, 69.5-NR) and 83.4 months (95% CI, 61.8-NR) [HR, 1.02; (95% CI, 0.67-1.55)]; $p=0.9$][59]. The CHAARTED phase III trial evaluated the role of docetaxel plus ADT (at a dose of 75 mg/m^2 every 3 weeks for six cycles) *vs.* ADT alone in 790 mCSPC patients prospectively stratified in low- and high-volume disease subgroups. At a median follow-up of 53.7 months, the median OS was 57.6 months for the chemo-hormonal arm *vs.* 47.2 months for ADT alone (HR, 0.72; 95% CI, 0.59-0.89; $p=0.0018$).

For patients with HV disease, the median OS was 51.2 months with chemo-hormonal therapy versus 34.4 months with ADT alone (HR, 0.63; 95% CI, 0.50 to 0.79; $p < 0.001$); for those with LV disease, no OS benefit was observed (HR, 1.04; 95% CI, 0.70 to 1.55; $p = 0.86$)[60,61]. Gravis et al[62] conducted a post-hoc analysis to demonstrate the OS benefit of ADT plus docetaxel *vs.* ADT alone in specific subgroups of patients from the CHAARTED and GETUG-AFU15 trial, according to metastatic volume burden (HV or LV) and time of metastasis occurrence [at diagnosis or after failure of local therapy (PRLT)]. This meta-analysis showed significant heterogeneity in ADT plus docetaxel *vs.* ADT effect sizes between HV and LV subgroups ($p = 0.017$), but no heterogeneity in ADT plus docetaxel *vs.* ADT effect sizes between upfront and after failure of prior local treatment subgroups ($p = 0.4$). Adding docetaxel in patients with HV-mCSPC disease has a consistent effect in improving median OS (HV-ADT: 34.4 and 35.1 months, HV-ADT + docetaxel: 51.2 and 39.8 months in CHAARTED and GETUG-AFU15, respectively (HR, 0.68; 95% CI, 0.56; 0.82, $p < 0.001$). LV patients showed longer OS, regardless docetaxel (LV-ADT: NR and 83.4 months; LV-ADT + Docetaxel: 63.5 months and NR in CHAARTED and GETUG-AFU15, respectively; HR, 1.38; 95% CI, 1.03-0.77). Pooled HRs showed significant improvement in OS from ADT plus docetaxel only in patients with HV disease and de novo metastases (HR, 0.67; 95% CI, 0.55-0.83). Conversely, pooled HRs showed no improvement in OS from ADT plus docetaxel in LV patients in both de novo metastatic and PRLT (HR, 1; 95% CI, 0.70-1.44 or HR, 1.12; 95% CI, 0.66-1.99, respectively)[62,63]. Recently, the STAMPEDE-DOCETAXEL trial enrolled high-risk, locally advanced, metastatic or recurrent CSPC patients to standard of care only (SOC-only; control), SOC plus zoledronic acid, SOC + docetaxel, or SOC + zoledronic acid + docetaxel). After a follow-up of 43 months, mOS was 71 months (IQR 32 to not reached) for SOC-only, not reached (32 to not reached) for SOC + zoledronic acid (HR, 0.94; 95% CI, 0.79-1.11; p=0.450), 81 months (41 to not reached) for SOC + docetaxel (HR, 0.78; 95% CI, 0.66-0.93; p=0.006), and 76 months (39 to not reached) for SOC + zoledronic acid + docetaxel (HR, 0.82; 95% CI, 0.69-0.97; p=0.022). There was no evidence of heterogeneity in treatment effect (for any of the treatments) across pre-specified subsets. A post-hoc analyses of STAMPED-DOCETAXEL trial, restricted to mCSPC and stratified according to CHAARTED criteria, showed significant benefit of docetaxel in addiction to ADT in terms of OS (HR, 0.81; 95% CI, 0.69-0.95, $p = 0.009$) with no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups ($p = 0.827$)[64].

Apalutamide

The phase III TITAN trial evaluated apalutamide at dose of 240 mg daily plus ADT *vs.* placebo plus ADT in 525 (62.7% with HV disease, and 37.3% with LV disease) mCSPC patients. The OS at 24 months was higher with apalutamide than with placebo (82.4% versus 73.5%, respectively; HR, 0.67; 95% CI, 0.51 to 0.89; p= 0.005). The analysis of the forest plot shows a clinical benefit in all subgroups, regardless of the volume of disease[65].

Enzalutamide

The phase III ENZAMET enrolled 1125 mCSPC patients, stratified by volume burden, to enzalutamide at dose of 160 mg daily plus ADT *vs.* ADT plus a standard non-steroidal antiandrogen drug. At median follow-up of 34 months, the estimated OS at 3 years was 80% in the enzalutamide group and 72% in ADT arm (HR, 0.67; 95% CI, 0.52 to 0.86; $p = 0.002$). All secondary endpoints have been reached, such as, PSA progression-free survival (HR, 0.39; p<0.001) and PFS (HR, 0.40; p<0.001)[66]. The phase III ARCHES trial randomized 1150 mCSPC patients stratified by disease volume and prior docetaxel chemotherapy to receive enzalutamide at standard dose plus ADT *vs.* ADT plus placebo. The study met its primary endpoint, the risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (HR, 0.39; 95% CI, 0.30 to 0.50; $p < .001$; median not reached versus 19.0 months), in all prespecified subgroups, including those with LV disease and/or prior docetaxel[67].

mCSPC Treatment: Debating

Several meta-analyses[68-75] have indirectly compared various systemic therapies in terms of OS benefit in mCSPC patients, suggesting that ADT in addition to docetaxel, abiraterone, enzalutamide or apalutamide, significantly prolong both FFS and OS compared to ADT alone[68]. The role of docetaxel in mCSPC is debated. A systematic review and meta-analysis[69] of the 3 trials (CHAARTED, GETUG-15, STAMPEDE) showed that the addition of docetaxel to standard

of care improved OS (HR, 0.77; 95% CI, 0.68-0.87; $p<0.0001$) with an absolute improvement in 4-year survival of 9% (95% CI, 5-14). There was also a significant advantage in terms of FFS (HR, 0.64; $p<0.0001$). Vale et al[70,71] conducted a network meta-analysis based on aggregate data from all available studies in CSPC, showing that abiraterone had the highest probability of being the most effective treatment both for OS (94% probability) and FFS (100% probability), while docetaxel was the second-best treatment for OS (35% probability). These data were confirmed by Kassem et al[72], who showed a better PFS (HR, 0.38; 95% CI, 0.34-0.43) and less toxicity for abiraterone plus ADT *vs.* docetaxel with ADT (HR, 0.634; 95% CI, 0.57-0.70) while the indirect comparison showed that the HRs of OS and PFS in docetaxel plus ADT group *vs.* abiraterone plus ADT were 1.2 (95% CI, 0.98-1.46) and 1.65 (955 CI, 1.40-1.94), respectively, without a significant difference in OS[71]. Feyerabend et al[73] conducted a systematic review of the aforementioned trials (LATITUDE, CHAARTED and GETUG-AFU 15) only for the newly diagnosed mCSPC, who fell in the HR and/or HV-mCSPC group. This review showed that abiraterone plus ADT was at least as effective as docetaxel plus ADT in reducing the risk of death, but better at preventing disease progression and improving QoL. To date, the combination therapy (ADT plus Docetaxel or Abiraterone or Enzalutamide or Apalutamide) represents the standard of care in High Volume mCSPC disease, but several questions remain about the role of such treatment in Low volume mCSPC. Chen et al[74] conducted a direct meta-analysis, suggesting that ADT plus docetaxel, or abiraterone, or enzalutamide, or apalutamide significantly improved OS and FFS *vs.* ADT alone in men with mCSPC. SUCRA analysis demonstrated the superiority of ADT plus abiraterone or enzalutamide over other therapies. Subgroup analyses indicated that abiraterone plus ADT had the highest ranking in patients with HV diseases or visceral metastases and enzalutamide plus ADT outperformed other treatments in patients with LV diseases or without visceral metastases. Recently, a systematic review and network meta-analysis[75], indirectly evaluated the OS in HR or HV-mCSPC treated with abiraterone plus ADT *vs.* docetaxel plus ADT. Overall, 6067 patients from five trials were included: 1181 (19.5%) patients received docetaxel plus ADT, 1557 (25.7%) patients received abiraterone plus ADT, and 3329 (54.9%) patients received ADT alone. The pooled HR for OS was 0.75 (95% CI, 0.63-0.91, I^2=51%, 3 trials, 2951 patients) for docetaxel plus ADT *vs.* ADT-alone and 0.63 (95% CI, 0.55-0.72, I^2=0%, 2 trials, 3116 patients) for abiraterone plus ADT *vs.* ADT alone. The indirect comparison of abiraterone plus ADT to docetaxel plus ADT demonstrated no statistically significant difference in OS between these approaches (HR, 0.84; 95% CI, 0.67-1.06), although Bayesian analysis demonstrated a high probability that abiraterone plus ADT was preferred. Similarly, a direct randomized comparative analysis of docetaxel plus ADT *vs.* abiraterone plus ADT in mCSPC showed no statistically difference in OS (HR, 1.16; 95% CI, 0.82-1.65)[75]. Conversely, Sathianathen et al[76] showed that enzalutamide plus ADT had the lowest absolute HR compared with ADT only (HR, 0.53; 95% CI, 0.37-0.75), and an estimated 76.9% likelihood that it was the preferred treatment to prolong OS compared with other combination treatments, or with ADT alone. Enzalutamide appeared to have better OS compared with docetaxel in men with LV disease, but there was no difference in other comparisons[77]. A subgroup analysis of all aforementioned trials, according to disease volume burden observed that:

1. HV subgroup, ADT plus abiraterone (HR, 0.62; 95% CI, 0.50-0.74), ADT plus apalutamide (HR, 0.68; 95% CI, 0.50-0.92), ADT plus docetaxel (HR, 0.73; 95% CI, 0.62-0.86), and ADT plus enzalutamide (HR, 0.64; 95% CI, 0.42-0.99) prolonged OS compared to ADT alone;
2. LV disease subgroup, all combined treatments showed an OS benefit over ADT monotherapy, but statistical significance was only observed for ADT plus enzalutamide (HR, 0.38; 95% CI, 0.21-0.69).

Moreover, stratifying patients according to Gleason Score, the authors showed that:

1. in Gleason score <8 subgroup, ADT plus apalutamide (HR, 0.56; 95% CI, 0.33-0.95) and ADT plus docetaxel (HR, 0.71; 95% CI, 0.54-0.92) were superior to ADT monotherapy;
2. in Gleason score ≥ 8 subgroup, all of the combined treatments were superior to ADT monotherapy; however, the differences were not statistically significant[77,78].

Finally, Marchioni et al[79] concluded that no treatment was superior to docetaxel in terms of OS in mCSPC. However, abiraterone (HR 0.89;

95% CI, 0.76-1.05), enzalutamide (HR, 0.90; 95% CI, 0.69-1.19) and apalutamide (HR, 0.90, 95% CI; 0.67-1.22) showed non statistically significant lower overall mortality rates than docetaxel. Abiraterone (HR, 0.71; 95% CI, 0.59-0.86), enzalutamide (HR, 0.61; 95% CI 0.49-0.75) and apalutamide (HR, 0.74; 95% CI, 0.57-0.95) also showed statistically significant lower disease progression rates than docetaxel, with enzalutamide (OR, 0.56; 95% CI, 0.35-0.92) and apalutamide (OR, 0.44; 95% CI, 0.24-0.79) demonstrated statistically significant lower rates of high-grade adverse events compared to docetaxel[78]. In summary, considering the volume disease burden (HV *vs.* LV) and the time of metastasis occurrence (*de novo vs.* after failure of local treatment) we identify 3 prognostic groups of mCSPC patients:

1. good prognosis for those with LV disease and systemic recurrence after failure of local therapy;
2. ntermediate prognosis for those with systemic recurrence after failure of local therapy and HV disease, or those with LV disease and *de novo* metastases;
3. poor prognosis for those with *de novo* HV disease.

Docetaxel plus ADT or NGARi (abiraterone-enzalutamide-apalutamide) plus ADT represents the standard of care for HV and HR-mCSPC, respectively. To date, there are no head-to-head trials, but if considering the reported HR for OS in the abiraterone trial (HR, 0.62 for STAMPEDE and 0.63 for LATITUDE), in the ENZAMET trial (HR, 0.67), in the TITAN trial (HR, 0.67) and in CHAARTED trial (HR, 0.63), they resulted quite similar but with different safety profile. For docetaxel, the data are most robust for patients with *de novo* HV-mCSPC, while we need additional data in LV-mCSPC. The use of NGRAi plus ADT are recommended for HR-mCSPC (per LATITUDE) or HV-mCSPC (for ENZAMET or TITAN), even if patients at LV may also be offered ADT and abiraterone (per STAMPEDE) or ADT and enzalutamide (per ENZAMET) or apalutamide plus ADT (per TITAN). According to the aforementioned trial, probably only patients who present with metastatic disease de novo (67% in GETUG-15, 73% CHAARTED, 60% in STAMPEDE-DOCETAXEL, 50% in STAMPEDE-ABIRATERONE, 100% in LATITUDE, and 16.2% in TITAN) rather than who develop metastases over a long period after failure of local therapy could really benefit from docetaxel or NGARi. The safety profile of single treatments (hematological toxicity for docetaxel, hypertension, cardiac disorder and ALT increase for abiraterone, fracture for apalutamide, dementia or seizures for enzalutamide) significantly influences the choice of treatment. Other clinical factors considered are: patients comorbidities or fitness, drug availability in various health care systems, QoL, and mostly, the duration of treatment, limited for docetaxel (6 cycles) versus continuous for abiraterone-enzalutamide-apalutamide (until progression or adverse events).

Low-Volume or Low-Risk mCSPC (Oligometastatic CSPC)

If it is clear that the addition of chemotherapy (docetaxel) or NGARi (enzalutamide-abiraterone-apalutamide) in HV or HR-mCSPC results in an advantage in OS, then, how to manage low-volume or low-risk CSPC? (Table II). The ADT remains the milestone, but several studies[79-82] suggested a possible advantage in OS adding RT to the prostate in de novo mCSPC classified as oligometastatic. The HORRAD phase III trial evaluated the addition of external beam radiation therapy (EBRT) of the prostate to ADT in 432 de novo mCSPC. The OS was not statistically different between the 2 groups with a mOS of 45 months in the group receiving EBRT (95% CI, 40.4-49.6) *vs.* 43 months in the control group (95% CI, 32.6-53.4). In a subgroup analysis, the mOS appeared more favourable in patients with less than 5 bone metastases (HR, 0.68; 95% CI, 0.42-1.10)[83-85]. The data from the STAMPEDE-RT study published by Parker et al[85] showed that in LV disease the addition of prostate RT to ADT produced a reduction in the risk of death of 32% (HR, 0.68; 95% CI, 0.52-0.90)[84-88]. In this context, Burdett et al[89] assessed the superiority of the association of prostatic RT to ADT compared to ADT alone in patients with mCSPC, analyzing the STAMPEDE, the HORRAD and the PEACE-1 trial. Although the addition of prostatic RT to the ADT did not result in an increase in OS compared to ADT alone (HR, 0.92; 95% CI, 0.81-1.04), a subgroup analysis observed that the effect of RT on the prostate in terms of OS varies according to the number of bone metastases, with a significant benefit in patients with less than 5 bone metastases (HR, 0.73; 95% CI, 0.58-0.92) and an absolute increase of 7% (95% CI, 2% -11%) in 3-year survival (from 70% to 77%)[88]. Recently, apart from RT, the use of NGRAi plus ADT in

LV or LR-mCSPC showed encouraging results, although studies comparing with RT are missing. Unfortunately, even if there is no clear definition of oligometastatic patients, in our opinion oligometastatic sub-group can be assimilated to the definition of low-volume or low-risk according to CHARTEED or LATITUDE definition, i.e., < 4 bone lesions and absence of visceral metastases. Clearly, the EBRT or NGRAi prolong OS in LV or LR-mCSPC patients, and if we consider the aforementioned studies, the advantage is only in those with low-volume disease and de novo metastases, previously defined as intermediate group mCSPC. The role of RT in low volume mCSPC relapsed after failure of local therapy (good prognosis), remains debated. Several studies[89-91] suggest a possible role of metastasis-directed therapy (MDT) for oligo-recurrent prostate cancer (PCa) after local treatment with curative intent. A phase II trial enrolled 62 asymptomatic PCa patients who had a biochemical recurrence with ≤ 3 extracranial metastatic lesions on choline positron emission tomography-computed tomography, to either surveillance or MDT of all detected lesions. At a median follow-up of three years, the primary outcome of median ADT-free survival was 13 months for the surveillance group and 21 months for the MDT group (HR, 0.60; 80% CI, 0.40-0.90, log-rank p=0.11)[92,93]. The MDT opens a new scenario, but more large prospective trials need to validate this approach. Recently, the introduction in clinical practice of the PSMA-PET allows to redefine the volume disease burden (low versus high) and thus to identify the true oligometastatic patients to benefit from local treatments[94].

Metastatic Castration Resistant Prostate Cancer (mCRPC)

The old definition of mCRPC identified patients who presented with biochemical and/or clinical and/or radiological progression despite castrate serum testosterone levels (<50 ng/dl or <1.7 nmol/l) on ADT. To date, with

the use of chemotherapy (docetaxel) or NGARi (abiraterone-enzalutamide-apalutamide) in HR or HV-CSPC, the old definition of CRPC remains inapplicable in most mPC and restricted to patients defined low-volume or low-risk in CSPC setting, where the ADT with or without RT represents the standard of care. In this paragraph we report the approved treatment, according to the old definition of CRPC. Several therapeutic options are available for this setting and include chemotherapy (docetaxel, cabazitaxel), next generation androgen receptor inhibitors (abiraterone, enzalutamide), radio compounds (Radium-223) and immunological therapies (Sipuleucel-T)[95,96] (Table IV).

Abiraterone

The phase III trial COU-AA-302 comparing abiraterone and prednisone *vs.* placebo and prednisone, in asymptomatic or pauci-symptomatic

Table IV. Reported RCTs in CRPC-M1.

Trial	Agents	Indication	N	HR for OS or other endpoint	OS (mon)
Chemotherapy					
§Tax-327[4]	ADT + DOC q 21	mCRPC	1005	0.76	18.9
§Prosty[94]	ADT + DOC q 15	mCRPC	177	1.3 (TTTF)	
§Tropic[5]	CBZ (25 MG/MQ)	mCRPC*	755	0.70	15.1
§Proselica[95]	CBZ (20MG/MQ)	mCRCC*	1200	1.024	13.4
AR inhibitors					
§Cou-aa-301[7]	ADT + ABI	mCRPC*	1195	0.65	14.8
§Cou-aa-302[6]	ADT + ABI	mCRPC**	1088	0.75	NR
§Affirm[9]	ADT + ENZA	mCRPC*	1199	0.63	18.4
§Prevail[8]	ADT + ENZA	mCRPC**	1717	0.71	32.4
Other					
§Alsymca[100]	Radium-223	mCRPC**	921	0.7	14.9
§Impact[97]	Sipuleucel-T	mCRPC**	512	0.73	25.8

*Post docetaxel; **Pre docetaxel.

untreated CRPC M1, showed a longer rPFS (16.5 months *vs.* 8.3 months; HR 0.53; 95% CI, 0.45-0.62; p <0.001]) and OS (34.7 months *vs.* 30.3 months, HR, 0.81; 95% CI, 0.70-0.93; $p = 0.003$)[6]. The COU-AA-301 evaluated abiraterone versus placebo in 1195 pre-treated (post-docetaxel) mCRPC patients. The mOS was 14.8 months in the abiraterone group *vs.* 10.9 months in the placebo group (HR, 0.64; 95% CI, 0.54-0.77; p <0.0001), with a longer rPFS (5.6 *vs.* 3.6 months; HR, 0.67; 95% CI, 0.58-0.78; p <0.001)[7].

Enzalutamide

The phase III PREVAIL enrolled 1717 untreated mCRPC patients (including visceral metastases). The trial showed a longer OS (35.3 months *vs.* 31.3; HR, 0.77, 95% CI, 0.67 -0.88; p = 0.0002) and rPFS (20 months *vs.* 5.3; HR, 0.32, 95% CI, 0.28-0.37; p <0.0001)[8]. The AFFIRM study[9] evaluated enzalutamide in 1199 pre-treated (post-docetaxel) mCRPC patients. After a median follow-up of 14.4 months, the median OS was 18.4 months in the enzalutamide group *vs.* 13.6 months in the placebo group (HR, 0.63; 95% CI: 0.52-0.75; p <0.0001) with a longer rPFS (8.3 *vs.* 2.9 months; HR, 0.40; 95% CI, 0.35-0.47; p <0.001)[9].

Docetaxel

The phase III TAX 327 enrolled 1006 untreated asymptomatic and symptomatic mCRPC patients to docetaxel with two different schedules (75 mg/m^2 three times a week or 30 mg/m^2 weekly) both in combination with prednisone (10 mg daily), *vs.* mitoxantrone (12 mg/m^2 three weeks) plus prednisone (10 mg daily). Docetaxel at dose of 75 mg/m^2 showed a significant advantage in OS (HR, 0.76; 95% CI, 0.62-0.94; p=0.009)[4]. Recently, a phase III trial compared the biweekly schedule of docetaxel (50 mg/m^2) *vs.* the standard schedule. It showed a significantly longer TTTF than 3-weekly administration (5.6 months, 95% CI, 5.0-6.2 *vs.* 4.9 months, 4.5-5.4; HR, 1.3; 95% CI, 1.1-1.6, p=0.014) with a lower incidence of grade 3-4 adverse events: neutropenia (53% *vs.* 36%), leukopenia (29% *vs.* 13%), and febrile neutropenia (14% *vs.* 4%)[97].

Cabazitaxel

The phase III TROPIC enrolled 755 pre-treated (post-docetaxel) mCRPC patients to cabazitaxel + prednisone versus mitoxantrone. There was a significant advantage in median OS (15.1 *vs.* 12.7 months, HR, 0.70; 95% CI, 0.59-0.83; p <0.0001) with a longer PFS (2.8 *vs.* 1.4 months, HR, 0.74; 95% CI, 0.64-0.86; p <0.0001)[5]. The PROSELICA study evaluated the non-inferiority of a reduced dose of cabazitaxel (20 *vs.* 25 mg/m^2 q21), demonstrating a similar mOS (13.4 *vs.* 14.5 months)[98,99].

Sipuleucel-T

The Sipuleucel-T has been the first immunotherapeutic agents approved in mCRPC. The phase 3 IMPACT trial showed a significant advantage in OS (25.8 *vs.* 21.7 months) in patients with minimally symptomatic or asymptomatic metastatic CRPC, with a 22% reduction in mortality risk (HR, 0.78; 95% CI, 0.61-0.98; p= 0.03). These data were subsequently confirmed by a prospective registry (PROCEED) with a mOS of 30.7 months (95% CI, 28.6-32.2 months). Benefit of Sipuleucel-T has not been reported in patients with visceral metastases[100-102].

Radium-223 (Xofigo)

The phase 3 ALSYMPCA trial evaluated the role of Radium-223 in symptomatic mCRPC patients with at least two symptomatic bone metastases and no known visceral metastases, showing a statistical longer mOS, regardless previous docetaxel use (previous docetaxel use, HR, 0.70; 95% CI, 0.56-0.88; p=0.002; no previous docetaxel use, HR, 0.69; 95% CI, 0.52-0.92; p=0.01). This study reached all the main secondary efficacy endpoints, particularly, significant longer time to first symptomatic skeletal event in previous docetaxel pre-treated patients[103]. Recently, the European Medicines Agency (EMA) has recommended restricting its use to patients who have had two previous treatments for mCRPC or who cannot receive other treatments, considering the negative results of the ERA 223 trial and the increased frequency of bone fractures in the combination arm (abiraterone plus radium-223) versus placebo[104-106].

mCRPC: Debating

To date, the use of NGARi (abiraterone or enzalutamide) in untread mCRPC (pre-docetaxel group) is restricted in asymptomatic or pauci-symptomatic patients. In order to delay the time to chemotherapy start (docetaxel), several studies[106-109] evaluated the role of a so-called "hyper-castration", namely a combination of anti-androgens of new generation (enzalutamide or apalutamide) with an androgen biosynthesis inhibitor (abiraterone). Different preclinical stud-

ies[110-115] showed that a prolonged use of antiandrogens, results in compensatory autocrine and paracrine androgenic biosynthesis. Unfortunately, the PLATO trial failed to demonstrate the efficacy of combination of enzalutamide and abiraterone in mCRPC. The median OS was 33.6 (95% CI 30.5-36.4) and 32.7 months (29.9-35.4) respectively, $p = 0.53$, with a treatment discontinuation due to AEs of 13% in the combination arm[106-108]. Subsequently, the ACIS trial evaluated the combination of anti-AR apalutamide plus abiraterone in chemo-naive mCRPC. The ACIS final analysis met the primary endpoint and demonstrated a 31% reduction in risk of radiographic progression or death, although it was not demonstrated a statistically significant longer OS, time to PSA progression, chronic opioid use, initiation of cytotoxic chemotherapy, and pain progression[109]. Generally, abiraterone, enzalutamide and cabazitaxel have shown to be effective in patients progressing after docetaxel treatment, regardless of the risk categories. Unfortunately, there are no direct comparison trials between these approved therapies. The treatment choice depends only to the previous treatments, response at previous treatments, patients' comorbidities or fitness, drug availability in various health care systems, QoL during previous treatment, and mostly, the duration of treatment (limited for docetaxel and cabazitaxel *vs.* continuous for abiraterone and enzalutamide). Safety profile of single drug (hematological toxicity for docetaxel and cabazitaxel, hypertension, cardiac disorder and ALT increase for abiraterone, dementia or seizures for enzalutamide) have a big choice role. Patients who have received first-line enzalutamide/abiraterone therapy, should be treated with docetaxel, while patients who progress to docetaxel treatments may have two alternatives: second line NGARi (enzalutamide/abiraterone) or cabazitaxel. Generally, in second line setting (post-docetaxel), patients should receive enzalutamide/abiraterone in case of good response to previous ADT (duration of response higher than 12 months), or who are asymptomatic/oligosymptomatic and with no visceral metastases. Conversely, patients should receive cabazitaxel in case of refractory to previous ADT (duration of response lower than 12 months) or who are symptomatic or with high-volume disease and/or visceral metastases[115,116]. The CARD trial compared cabazitaxel with either abiraterone or enzalutamide in patients with mCRPC who had previously received docetaxel (at least 3 cycles) and who had disease progression within 12 months on abiraterone or enzalutamide treatment (before or after docetaxel therapy). After a follow-up of 9.2 months, the median imaging-based progression-free survival was 8.0 months with cabazitaxel and 3.7 months with abiraterone/enzalutamide. The median OS was 13.6 months with cabazitaxel and 11.0 months with abiraterone/enzalutamide (HR, 0.64; 95% CI, 0.46 to 0.89; p=0.008), with a mPFS of 4.4 *vs.* 2.7 months, respectively (HR, 0.52; 95% CI, 0.40 to 0.68; p<0.001); the PSA response was 35.7% and 13.5%, respectively (p<0.001) with a RR of 36.5% *vs.* 11.5% (p=0.004)[117]. In patients with symptomatic bone metastases, Radium-223 should be offered, after at least two previous treatments for mCRPC. Finally, all patients with bone metastases have to receive osteoclast-targeted agents to reduce the rate of skeletal related events (SRE).

Therapeutic Strategy in Docetaxel or NGARi Pre-Treated HV and/or HR-mCSPC Patients Who Progress to CRPC

The impact of upfront docetaxel or NGARi on subsequent therapies is still unexplored. Undoubtedly, high-risk or high-volume CSPC treated with chemotherapy (Docetaxel) or NGARi (Abiraterone-Enzalutamide-Apalutamide) continue ADT and more than 50% of them receive at least one subsequent treatment as they progress to CRCP. In the CHAARTED trial, of the 238 patients who had progressed on ADT plus docetaxel, 150 received one or more treatments including: docetaxel rechallenges, cabazitaxel, abiraterone, or enzalutamide, and of 287 ADT-alone patients, 187 had received one or more of these agents. In the apalutamide trial subsequent life-prolonging therapy was received by 371 (46%) patients in the apalutamide arm and by 338 (84%) patients in the placebo group, including 59 patients who received apalutamide after crossover. Retrospective data from the GETUG-AFU 15 phase 3 trial were collected to identify the treatments received in CRPC setting. Overall, 245 patients received at least one treatment for mCRPC. 127 of 149 patients (85%) from the ADT arm received docetaxel (91% in the HV disease and 78% in the LV disease subgroup). Other treatments administered were abiraterone acetate (36 and 33 in the ADT and ADT plus docetaxel arms, respectively), cabazitaxel (15 and 16 patients, respectively), and enzalutamide

(12 and 15 patients, respectively). For docetaxel used in first line, a PSA decline ≥50% was observed in 25/66 (38%) and in 4/20 patients (20%) who had received upfront ADT alone and ADT plus docetaxel (p=0.14). The median biochemical PFS was 6.0 (95% CI, 3.6-7.7) and 4.1 months (95% CI, 1.3-4.9), respectively. For docetaxel used in first- or second line, a PSA decline ≥50% was observed in 36/80 (45%) and in 4/29 patients (14%) who had received upfront ADT alone and ADT plus docetaxel (p=0.07). PSA declines to ≥50% were observed with bicalutamide in 12/28 (43%) and 4/23 patients (17%) who had received upfront ADT alone and ADT plus docetaxel. Among men treated upfront with ADT plus docetaxel who received abiraterone or enzalutamide for mCRPC, 10/19 patients (53%) achieved a PSA decline ≥50%. Docetaxel rechallenges showed limited activity, while available data on abiraterone and enzalutamide confirms their efficacy in this setting[118]. Francini et al[119] evaluated the efficacy of abiraterone or enzalutamide in a cohort of patients previously treated with ADT plus docetaxel in CSPC setting (CHARTEED criteria). Of the 102 patients with mCRPC identified, 50 (49%) had previously received ADT alone, while 52 (51%) ADT plus docetaxel. No statistically significant difference in any of the evaluated outcomes was observed. It is interesting how, in the ADT-alone group, OS from abiraterone/enzalutamide start was shorter [17.3 months (95% CI, 13.7 months to NR)] than observed with pre-chemotherapy abiraterone and enzalutamide for mCRPC in the final analyses of their pivotal trials [34.7 months (95% CI, 32.7-36.8 months) and 35.3 months (95% CI, 32.2 months to NR), respectively][119]. Barata et al[120] retrospectively evaluated 136 mCRPC patients, pre-treated with at least 3 cycles of docetaxel-ADT (CHAARTED criteria) in mCSPC setting. The primary endpoints included rPFS and OS with first-line treatment for mCRPC. Median time to CRPC (biochemical, clinical, or radiographic) was 19.6 months (16.6-22.6). Sixty patients (44%) received ≥1 treatment for CRPC: 48 patients (80%) received a NGARi. Among these, 22 received abiraterone acetate, 20 enzalutamide, and six a novel CYP-17 inhibitor on trial (ASN-001). Five patients (8%) received sipuleucel-T; 4 (7%) radium-223, 5 (8%) chemotherapy (2 carboplatin-based, 2 cabazitaxel, 1 docetaxel) and 3 others. Patients receiving NGARi had a median rPFS of 9.0 months (95% CI, 6.9-11.2) compared with 3.0 months (95% CI, 1.5-4.5) for patients who received a non-NGARi treatment (p = 0.024). The choice of first therapy for mCRPC was independent of Gleason Score (p = 0.909), visceral disease (p = 0.690) and time to CRPC (p = 0.844). Longer OS correlated with time to CRPC (p = 0.010) and first treatment for CRPC with NGARi (p = 0.005). For patients with progressive disease on docetaxel-ADT, subsequent treatment with a NGARi was associated with a longer rPFS and OS[120]. Finally, Schmidt et al[121] published a retrospective analysis of 93 patients pre-treated with docetaxel-ADT in the mCSPC setting; in this analysis the median time to mCRPC (biochemical, clinical or radiographic) was 14.8 months (95% CI, 11.9-16.5). 1L treatment was enzalutamide in 47 (55%), abiraterone in 23 (27%), cabazitaxel in 7 (8%), docetaxel in 4 (5%) and other therapies in 4 patients (5%). Median 1L TTF was 6.3 months (95% CI, 4.9-7.6), PSA > 50% reduction was achieved in 32 of 89 patients (36%), median time from 1L to second-line treatment was 7.3 months (1.3-27.4), which did not differ significantly between treatment groups[121]. To date, there was no robust evidence to define the best next step for patients progressing to CRPC after ADT plus docetaxel (CHAARTED) or NGARi (Abiraterone per LATITUTE, Enzalutamide per ENZAMET or Apalutamide per TITAN). Patients, who progress on NGARi (Abiraterone-Enzalutamide-Apalutamide), regardless of other risk factors, are easily candidates for chemotherapy (docetaxel) as in the CRPC setting, but it is more complex for patients progress after docetaxel treatments in mCSPC. In this sub-group the best sequential treatment is influenced by several factors, including clinical, molecular and patient-reported adverse events. Tucci et al[122] indicate the PFS to previous treatment (docetaxel-CHAARTED) as the most important parameter to consider in subsequent therapies. Therefore, patients whose PFS is > 20 months on previous docetaxel could reasonably have experienced the greatest benefit from docetaxel treatment in mCSPC setting, hence, they should be considered sensitive to this treatment and, could be managed with a docetaxel rechallenge or in alternative abiraterone/enzalutamide especially, in case of severe adverse events during previous docetaxel. Conversely, patients who experienced shorter PFS, and therefore suffering from a more aggressive disease, cabazitaxel could be the best treatment, also considering the efficacy of this drug in refractory-docetaxel treatment (TROPIC). Patients who progress with asymptomatic

Table V. Setting-matched therapeutic strategies.

Biological	Imaging*	Clinical		Sub-group	Recommendation
CSPC	nmCSPC				Orchiectomy LHRH agonist ± AA LH RH antagonist
	mCSPC			Low Volume[1] High Volume[2] High Risk[3] All Comers[4]	Continuous ADT ± RT* Continuous ADT + Apalutamide Continuous ADT + Enzalutamide Continuous ADT + Docetaxel × 6 cy Continuous ADT + Abiraterone Continuous ADT + Apalutamide Continuous ADT + Enzalutamide
CRPC	nmCRPC			High Risk[5]	Continuous ADT + Apalutamide Continuous ADT + Enzalutamide Continuous ADT + Darolutamide
	mCRPC	First-Line	Asymptomatic Mildly symptomatic Symptomatic		Abiraterone Enzalutamide Docetaxel Docetaxel
		Second-Line	Post-ABI/ENZA Post-Docetaxel	 HRR Gene Mutation	Docetaxel Enzalutamide/Abiraterone Olaparib Abiraterone/Enzalutamide Cabazitaxel
		Third-Line			Cabazitaxel Abiraterone/Enzalutamide

[1-2]CHAARTED criteria; [3]Latitude criteria; [4]Titan citeria; [5]Spartan/prosper/aramis criteria. *Standard Imaging: CT and Bone Scan.

or pauci-symptomatic disease, especially if after a long interval on ADT treatment (≥ 12 months) and with a PSADT ≥ 6 months, could benefit from abiraterone/enzalutamide treatment. Conversely, for patients who experienced only biochemical (PSA) progression, considering the robust PSA-response registered in the COU-AA-301 and AFFIRM trials, enzalutamide and abiraterone could be the treatment of choice. In the intermediate group (PFS greater than 12 months), we can consider different option. according to patient's reporting adverse event on previous therapy in mCSPC (hematological toxicity for docetaxel and cabazitaxel), ECOG performance status, comorbidities (hypertension, cardiac disorder and ALT increase for Abiraterone, fracture for Apalutamide, dementia or seizures for Enzalutamide), and poor features such as visceral metastases, high level of ALP, LDH or shorter duration of prior ADT. In case of progression with visceral metastases, especially liver metastases, chemotherapy (cabazitaxel and re-challenge with docetaxel in case of PFS > 20 months) could represent the first choice, although enzalutamide could be assessed (AFFIRM trial)[123,124].

Conclusions

The therapeutic armamentarium for systemic prostate cancer is rapidly evolving. The introduction of a new concept of systemic disease: high risk or high volume *vs.* low risk and low volume disease CSPC has further reshuffled the cards, diversifying the use of previously approved drugs in CRPC and opening a new scenario for sequence therapies (Table V). To date no prospective randomized trials published and only clinical factors, such as the presence of symptoms, biochemical or clinical or overt radiographic progression, prior therapies and durability of initial chemo-hormonal or ADT response, can trace the path. Prospective studies are warranted, considering the recent progress on immunotherapy and PARPi.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contribution
Conceived and designed the review: Carmine D'Aniello, Carla Cavaliere and Gaetano Facchini. Wrote the paper: Carmine D'Aniello, Carla Cavaliere and Gaetano Facchini. All the authors contributed to the research of the published articles and reviewed the manuscript.

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