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NOVEL THERAPEUTIC APPROACH TO METASTATIC HORMONE-SENSITIVE PROSTATE CANCER – THE CURRENT LANDSCAPE

ARTIGO DE REVISÃO NARRATIVA

ÁREA CIENTÍFICA DE UROLOGIA

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1. ABSTRACT

Introduction: After decades of a single regimen treatment for metastatic hormone-sensitive prostate cancer (mHSPC), the treatment landscape shifted and expanded in a short period of time. This rapid change entailed significant difficulties for clinicians to keep up to date with literature and data to perform evidence based and patient centered treatment decisions.

Methods: A comprehensive narrative review was conducted of all new treatment options for patients with mHSPC as of 2020. The focus were phase II/III randomized control trials addressing the role of new chemo and hormone therapies compared to previous gold-standard treatment.

Results: An overview of the trials investigating docetaxel (GETUG-AFU 15, CHAARTED, STAMPEDE Arm-C), abiraterone acetate (LATITUDE, STAMPEDE Arm-G), enzalutamide (ARCHES, ENZAMET) and apalutamide (TITAN) was performed. Furthermore, the role of volume disease, cost-effectiveness and adverse-events with these treatments were also evaluated. Available data supports an overall survival (OS) benefit with the addition of any of these 4 regimens compared to androgen deprivation therapy (ADT) alone, with similar efficacies among them. Volume disease plays a determinant role, as low-volume disease (LVD) patients do not appear to benefit as consistent from these new treatments as high-volume disease (HVD) patients. Cost-effectiveness, although not influencing the clear benefits in all endpoints researched, might play a role dependable of the patient and health system economic background, between treatments with similar results. Adverse events (AE) are common in chemotherapy regimens and patient-clinician choice of treatment must take this issue into consideration.

Conclusions: This new fast evolving reality forces clinicians to be proactive to provide evidence-base options of treatment for their patients. The majority of these novel therapies offer benefits without significant clinical differences between them, but data is being released at a fast pace, several individual factors must always be taken into consideration and recurrent reviews of the literature is a must for the upcoming decade.

Keywords: metastatic hormone-sensitive prostate cancer, androgen deprivation therapy, docetaxel, abiraterone acetate, enzalutamide, apalutamide.

2. RESUMO

Introdução: Após décadas de tratamento com um único esquema para o cancro da próstata metastizado hormono-sensível (CPmHS), o cenário mudou e expandiu-se num curto período de tempo. Esta rápida mudança acarretou dificuldades significativas para os médicos urologistas se manterem atualizados com a nova literatura para realizarem decisões terapêuticas baseadas na evidência e centradas no doente.

Métodos: Foi realizada uma revisão narrativa abrangente de todas as novas opções terapêuticas para pacientes com (CPmHS) até 2020. O foco recaiu em ensaios clínicos randomizados de fase II/III abordando o papel de novos fármacos de quimioterapia em comparação com a terapia “gold-standard” anteriormente realizada.

Resultados: Procedeu-se a uma revisão geral dos ensaios clínicos que investigaram docetaxel (GETUG-AFU 15, CHAARTED, STAMPEDE Arm-C), acetato de abiraterona (LATITUDE, STAMPEDE Arm-G), enzalutamida (ARCHES, ENZAMET) e apalutamida (TITAN).. Além disso foi avaliado o papel do volume da doença, custo-efetividade e efeitos secundários com estes fármacos. Os dados suportam um benefício da sobrevivência global com a adição de qualquer uma destas 4 terapêuticas em comparação com a hormonoterapia isolada, com eficácia semelhante entre eles. O volume da doença desempenha um papel importante, onde os pacientes com doença de baixo volume não aparentam beneficiar tão consistentemente comparativamente com os pacientes com doença de alto volume. A relação custo-efetividade, embora não influencie os benefícios claros em todos os parâmetros clínicos e estatísticos estudados, pode desempenhar um papel relevante consoante o contexto económico tanto do paciente como dos sistemas de saúde. Os eventos adversos são frequentes em regimes de quimioterapia e a escolha do tratamento pelo paciente e pelo médico deve ter sempre esta variável em consideração.

Conclusões: Esta nova realidade em rápida evolução obriga os médicos a serem proativos a fim de fornecer opções de tratamento baseadas na evidência aos seus pacientes. A maioria destes novos fármacos oferece benefícios sem diferenças clínicas significativas entre eles, mas o ritmo acelerado com que nova literatura é divulgada e os diversos fatores individuais de cada caso clínico, obrigam a uma decisão terapêutica complexa e mutável. Revisões recorrentes da literatura serão uma necessidade na próxima década.

Palavras-chave: cancro da próstata metastizado hormono-sensível, terapia de privação androgénica, docetaxel, acetato de abiraterona, enzalutamida, apalutamida.

3. ABBREVIATIONS USED:

AA – Abiraterone Acetate

ACE-27 - Adult Comorbidity Evaluation 27

ADT – Androgen Deprivation Therapy

AE – Adverse Events

AR – Androgen-Receptor

bPFS – Biochemical Progression-Free Survival

BPI-SF - Brief Pain Inventory–Short Form

CI – Confidence Interval

cPFS – Clinical Progression-Free Survival

EAU - European Association of Urology

ECOG - Eastern Cooperative Oncology Group

FACT-P - Functional Assessment of Cancer Therapy – Prostate

FFS – Failure-Free Survival

HR – Hazard Ratio

HVD – High Volume-Disease

ICER - Incremental Cost-Effectiveness Ratio

LHRH - Luteinizing Hormone-Releasing Hormone

LVD – Low Volume-Disease

mCRPC – metastatic Castration-Resistant Prostate Cancer

mHSPC – metastatic Hormone-Sensitive Prostate Cancer

mPFS – metastatic Progression-Free Survival

NE – Not Estimated

NR – Not Reached

OR – Odds Ratio

ORR – Objective Response Rate

OS – Overall Survival

PCa – Prostate Cancer

PCSS – Prostate Cancer Specific Survival

PFS – Progression-Free Survival

PRO – Patient-Reported Outcomes

PSA – Prostate Specific Antigen

QALY - Quality-Adjusted Life-Year

QoL – Quality of life

rPFS – Radiographic Progression-Free Survival

SOC – Standard-of-Care

SRE – Skeletal-Related Events

WHO – World Health Organization

4. INTRODUCTION

Prostate cancer (PCa) is the most diagnosed malignant neoplasm across male population in Portugal (1) , being projected to be the third cause of cancer deaths in the European Union in 2020 (2). However, the death rate trend has been declining since 1990, with a 7,1% decline expected from 2015 to 2020 (2), mainly due to advances in diagnosis and treatment (3). PCa is characterized by abnormally dividing cells in the prostate gland resulting in atypical prostate gland growth. Most of the male population will not die from PCa but will, either be affected by a slow-rate growing tumor or live the expected life expectancy because of progressively improving and effective treatment solutions. Death from prostate cancer, in most cases, occurs due to metastasis where cancer cells spread to other areas of the body, such as the pelvic and retroperitoneal lymph nodes, the spinal cord, bladder, rectum, bone and brain (4).

PCa patients can present metastatic disease recurrence after local treatment but can also show de novo metastatic disease without prior procedures such as radical prostatectomy or radiotherapy. Even though the timing of metastatic presentation might differ, the great majority of patients respond to surgical or medical castration, which is known as hormone-sensitive prostate cancer (mHSPC), also known as metastatic castrate-sensitive or hormone-naïve disease (5). Since the 1940s, ADT (6), which attempts to achieve castrate levels of testosterone, has been the backbone and the only form of treatment available for mHSPC, prior to the development of resistance and progression to metastatic castration-resistant prostate cancer (mCRPC), which has poorer diagnosis (5, 7). However, median duration of sensitivity to ADT is usually 24–36 months, with a median overall survival of about 30 months (95%, CI 12–53) (8, 9). Recently, the addition of novel androgen-receptor (AR) antagonists, previously used in the treatment of mCRPC (10), initiated with Docetaxel in 2015 (11, 12), and later with Abiraterone Acetate (AA) (13, 14), Enzalutamide (15, 16) or Apalutamide (17), have progressively become the treatment of choice for mHSPC.

As we are experiencing a sudden growth in differentiated treatment supply after several decades of stagnation, there is an imperative necessity to evaluate and compare their outcomes, such as OS, failure-free survival (FFS),clinical skeletal-related events (SRE), progression-free survival (PFS) or prostate cancer–specific death. Even more considering the significant gap in cost-effectiveness between these novel treatments, which in the current state of the world economy, is also worth considering (18).

The purpose of this study is to evaluate and compare if the new hormone and chemotherapy based therapies show an effective delay in the emergence of castration resistance and a relevant improvement in key outcomes like OS, FFS, SRE or PFS. Our aim

is, thereby, to determine, if the adding of these treatments to first-line treatment, instead of traditional ones (ADT), bring the expected benefits and to compare, between them, which one is more suitable for a given circumstance.

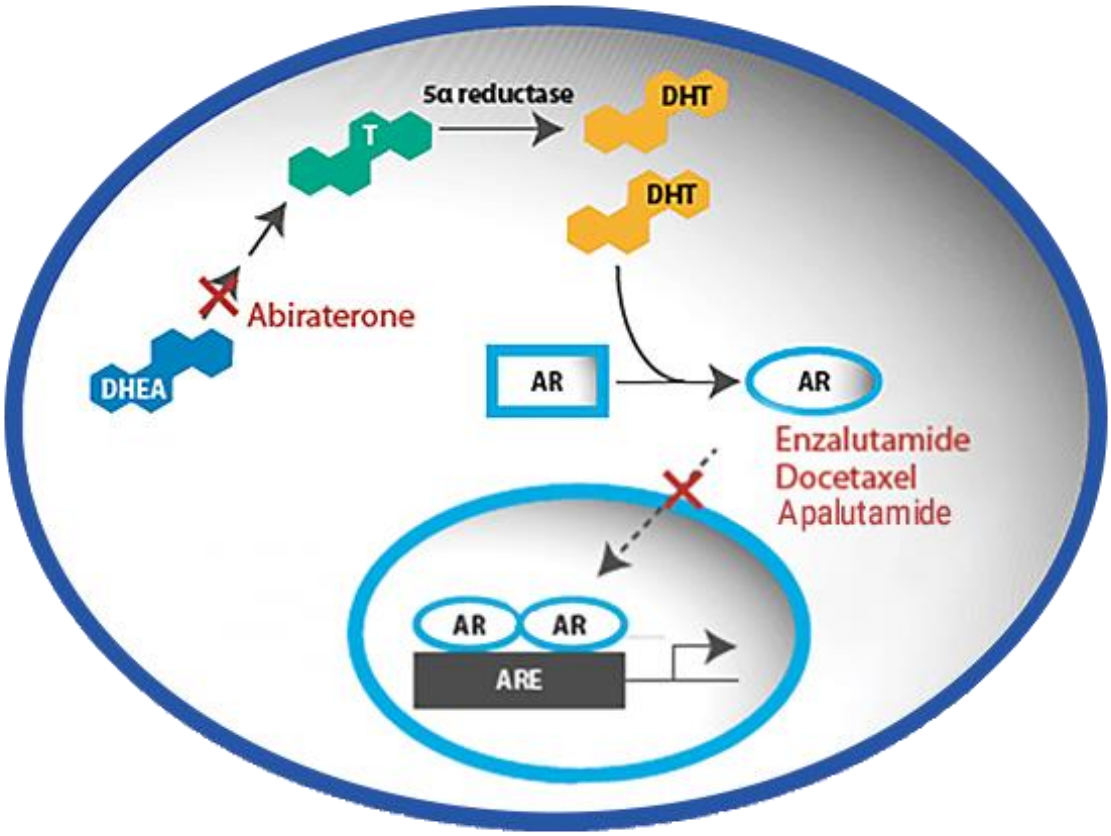

Figure 1. Graphical representation of intracellular androgen signaling and mechanism of blockade. In red are therapies to block androgen receptor signaling. ARE – androgen response element. DHEA – dihydroepiandrostenedione. DHT – dihydrotestosterone. T – testosterone. Figure adapted from (19).

5. METHODS

An online search was performed at Pubmed, using the keyword “metastatic hormone-sensitive prostate cancer” or “metastatic castrate-sensitive prostate cancer” in combination with “treatment”, “androgen deprivation therapy”, “docetaxel”, “abiraterone acetate”, “enzatulamide” and “apalutamide” to ensure complete results for pharmacotherapies in this disease environment.

The resulting original and review articles were analyzed, where more recent articles were preferably chosen, nonetheless the rest were not excluded. Priority was also given to recent review articles, which addressed the various aspects of metastatic hormone prostate cancer. The bibliographic references of the selected articles were also analyzed.

6. RESULTS

6.1 DOCETAXEL

Docetaxel, which is a taxane-based chemotherapy agent used to treat a variety of solid tumors, phosphorylates bcl-2 in vitro, leading to its inactivation and to subsequent cell death by apoptosis (Figure 1), started to demonstrate benefits in men with mCRPC in the beginning of this millennium (20)-(21, 22). However, not only until 2013, with the release of the first phase III trial regarding the use of Docetaxel alongside ADT in an earlier spectrum of the disease, the GETUG-AFU 15 (9), and later, with the trials CHAARTED (12) and STAMPEDE (11), concise and reliable conclusions were able to be established.

The GETUG-AFU 15 French trial enrolled 378 patients based on these underlined requirements: aged 18 years or more; histologically confirmed prostate adenocarcinoma and radiologically proven metastatic disease; Karnofsky score of at least 70%; life expectancy greater than or equal to 3 months; adequate hepatic, hematological, and renal function. Patients who previously had received chemotherapy for metastatic disease were excluded, but patients with metastatic disease could have initiated ADT treatment no more than 2 months before enrollment. Patients were randomly allocated to receive treatment with ADT alone (orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists with/without nonsteroidal androgen receptor inhibitors) or ADT plus docetaxel, where a 75mg/m2 intravenous doses was given at the very first day of each cycle (which lasted 21 one days each), for up to 9 cycles. The primary endpoint was OS (considered the best endpoint to assess the outcome of anticancer treatments — particularly in prostate cancer). Secondary endpoints were clinical progression-free survival (cPFS), and biochemical progression-free survival (bPFS). (9)

With a median follow-up of 50 months, the results did not show a median OS difference between ADT alone vs ADT plus docetaxel (54.2 months vs 58.9 months, Hazard Ratio: (HR) 1.01, 95% confidence interval (CI), 0,75–1,36, p=0,955). However, secondary endpoints, such as median bPFS and cPFS were significantly longer in the group that received ADT plus docetaxel. (9)

A post-hoc analysis was released a couple of years later, where the CHAARTED definition of HVD/LVD (later explained) was applied leading to an update in the survival analyses. A total of 385 patients was this time considered, having 48% of them HVD and 52% LVD. With a medium follow-up of 83.9 months, the median OS of the overall population kept being statistically-wise not significantly different between both groups (48.6 months vs 62.1 months, HR 0.88, 95% CI, 0,68-1,14, p=0,3). In the HVD and LVD subgroups comparisons,

the difference was, once again, not statistically significant (HR: 0.78, 95% CI, 0.56–1.09, p=0.14; HR: 1.02, 95% CI, 0.67–1.55, p=0.9; respectively). Secondary endpoints, bPFS and cPFS, did show benefits with docetaxel therapy in the overall survival (22.9 months vs 12.9 months, HR 0.67, 95% CI, 0,54-0,84, p<0,001; 22.9 months vs 15.3 months, HR: 0,69, 95% CI, 0,55-0,87, p=0,002; respectively), but when comparing subgroups HVD vs LVD, the results only displayed a clear statistically advantage in the HVD one, for both endpoints. (9)

Although being the first phase 3 trial using the combination of docetaxel-based chemotherapy and ADT in mHSPC and even though most of the secondary endpoints had encouraging results, there was no difference in median OS between both treatments. The post hoc analysis tried to explain these results as new trials were being released, being the most consensual that this study was underpowered to study the effect of docetaxel and that it included a higher percentage of patients with less aggressive disease (approximately half [43%] of the patients had Gleason scores ≤7). (9, 23)

Couple years after, the CHAARTED US trial results were published. This study consisted of 790 eligible patients assigned at a 1:1 ratio to ADT alone versus ADT plus docetaxel with a dose of 75 mg/m2 every 3 weeks for up to six cycles without daily prednisone. Patients were randomly stratified according to age (< 70 years vs ≥70 years), an Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1 vs 2), duration of prior adjuvant therapy with ADT (> 12 months vs ≤ 12 months), planned use of combined androgen blockade for > 30 days, usage of treatments to prevent skeletal related events (such as, zoledronic acid or denosumab) and proper renal, hematologic, and hepatic function. The main stratification factor was disease volume (high vs low), being HVD defined as presence of visceral metastases or more than 4 bone lesions with more than 1 beyond the spine and the pelvis (Figure 2). Primarily, only patients with HVD were enrolled but patients with LVD were included afterwards, after a prospectively stratification based on the volume of disease. It is also worth mentioning that neither dose modification nor intermittent ADT was permitted. The primary endpoint studied was OS, while secondary endpoint was time to development of mCRPC (12, 23-25).

The early results did show a median OS increase of 13,6 months between ADT alone and ADT plus docetaxel (44.0 months vs 57.6 months) - (HR 0.61, 95%, CI 0.47–0.80, p<0.0001). Between subgroups HVD vs LVD, which were prospectively stratified, a longer median follow-up of 53,7 months only showed an OS relevant benefit of 16,8 months in the first subgroup (median OS, 51.2 vs 34.4 months, HR 0.63, 95% CI 0.50 to 0.79, p<0.001). However, the LVD subgroup showed no survival advantage (median OS 63.5 months, HR 1.04; 95% CI, 0.70 to 1.55; p=0.86). Apart from these results, secondary endpoints like the prostate specific antigen (PSA) value, after 7 months of treatment, correlated itself with OS and was significantly longer for patients with a PSA less than 0.2 ng/dL compared with greater

than 4 ng/dL (60.4 vs. 22.2 months; P<0.001). If men received docetaxel, they were significantly more likely to reach a PSA of less than 0.2 ng/dL (45.3% vs. 28.8%; odds ratio (OR), 2.58; 95% CI, 1.82–3.64; p<0.001). 16.7% of all patients had a grade 3 AE, 12.6% grade 4 and only 1 patient had a grade 5 AE. These results are coherent with previous literature (26).

Around the same period, data from a multi-arm, multi-stage United Kingdom trial, named STAMPEDE was published assessing the role of docetaxel in mHSPC. In this cohort, 592 patients were treated with ADT plus docetaxel with 75 mg/m2 IV every three weeks, for 6 cycles (plus prednisone). The eligibility requirements of arm C not only included patients with metastatic disease (like the previous trials) but also patients with high-risk, locally advanced, and node-positive disease, fit for chemotherapy and could have received prior local treatment relapsing now with high risk features. Moreover, maintenance prednisone was administered 5 mg twice a day along with docetaxel, mirroring the treatment protocol in the castrate-resistant setting, which is also a unique feature from this trial. High-risk patients had at least 2 of the following 3 features: T3/4, Gleason 8-10, and PSA≥40 ng/mL (11).

The primary endpoint was OS, whereas secondary outcomes were the following: FFS, PFR, metastatic progression-free survival (mPFS) and prostate cancer specific survival (PCSS). Biochemical progression was evaluated using PSA measurements which were reported at each follow-up visit (11).

A significant improvement of 10 months was observed in median OS (81 months vs. 71 months, HR: 0.78, 95% CI, 0.66–0.93, p=0.006) and in median FFS (37 months vs 20 months, HR: 0.61, 95% CI, 0.53–0.70, p<0.001) compared to 1184 patients who received ADT alone. When evaluating metastatic patients only, the OS benefit appeared to be greater (60 months vs 45 months, HR: 0.76, 95% CI 0.62–0.92), which represented 61% of all patients in both arms. It is worth noticing, that the addition of zoledronic acid (used in different arms) was not noted to improve OS, consistent with the findings of other series (11).

Subsequently, a meta-analysis published in the European Association of Urology (EAU) combined the data from these 3 major phase III trials with the goal of evaluating the OS a PFS, regarding the addition of docetaxel in early setting of mHSPC. This meta-analysis concluded that not only the OS improved statistically, but there was also a clear benefit clinical-wise. ADT plus docetaxel was associated with a 27% reduction in the risk of death in patients with metastatic disease (HR: 0.73, 95% CI, 0.60–0.90; p=0.002), and the reduction in the risk of death is 33% in patients with HVD (HR: 0.67, 95% CI, 0.51–0.88). However, there was not a significant difference between disease volume and treatment efficacy. Concerning PFS, patients with metastasis did show statistically significant benefit in PFS (HR: 0.63; 95% CI, 0.57–0.70; p<0.001) when docetaxel was added to ADT treatment. The same benefit was

shown considering the whole study population which includes the marginal number of patients without metastases (HR: 0.63; 95% CI, 0.57–0.70; p<0.001). (27)

As for treatment toxicity, docetaxel, as an intravenous chemotherapy, is hard to tolerate for patients with poor performance status, advanced age, or preexisting comorbidities. During treatment, nausea, fatigue, neutropenia, and neuropathy were the most common side effects. Dose reduction was needed in 11% of the patients in the GETUG-AFU 15 trial, whereas in the CHAARTED trial, 26% of all intervened ones required dose reduction. The STAMPEDE trial did not provide data regarding this subject. Concerning treatment related deaths, even though the records were minimal (4 in the GETUG-AFU 15 and 1 in CHAARTED trial), older patients (>70 years), which are common in clinical practice, were underrepresented in all 3 trials. In any case, chemotherapy toxicity is often worse in the real-world population compared with the toxicity reported in clinical trials. Patients who receive docetaxel need, thereby, to be considered fit and eligible for chemotherapy (9, 11, 23-26, 28).

A resumed comparison with the most significant characteristics and results from these trials is shown below in Table 1.

Table 1. Selected Completed Clinical Trials Investigating Docetaxel in mHSPC.

Study characteristics	**GETUG-AFU 15 – POST-HOC ANALYSIS (28)**	**CHAARTED (12)**	**STAMPEDE - ARM C (11)**
Treatments used	ADT + docetaxel - 75 mg/m2; every 3 weeks; up to 9 cycles vs ADT	ADT + docetaxel - 75 mg/m2; every 3 weeks; up to 6 cycles vs ADT	ADT + docetaxel - 75 mg/m2; every 3 weeks; up to 6 cycles; Prednisone 5 mg twice daily; given for 21 days vs ADT
Eligibility Criteria	- Age ≥ 18 years - mHSPC - Karnofsky score ≥ 70% - Life expectancy ≥ 3 months - Adequate hepatic, haematological, and renal function	- mHSPC - ECOG 0–2	- Newly diagnosed mHSPC/node positive/high risk locally advanced (with ≥2 of T3/4, Gleason score of 8–10, PSA ≥40 ng/mL) - Prior local treatment, now relapsing with high-risk features - Fit for chemotherapy
Patients (n; experimental arm/comparable arm)	378 (188/190)	790 (397/393)	1776 (592/1184)
Disease characteristics – Volume Disease (HVD%/LVD%; n – HVD/ n – LVD)	48%/52% (92/100)	75%/35% (277/513)	54%/46% (148/124) – applied only for M1 patients

Primary Endpoints (experimental arm vs comparable arm)	OS: - All patients: 62.1 vs. 48.6 mo; HR, 0.88; 95% CI, 0.68-1.14 p=0.3 - HVD: 39.8 vs. 35.1 mo; HR, 0.78; 95% CI, 0.56-1.09, p<0.14 - LVD: Not reached (NR) vs 83.4 mo; HR 1.02; 95% CI, 0.67–1.55; p=0.9	OS: - All patients: 57.6 vs. 44 mo; HR, 0.61; 95% CI, 0.47-0.8; p<0.0001 - HVD: 51.2 vs. 34.4 mo; HR, 0.63; 95% CI, 0.50–0.79, p<0.001 - LVD: HR 1.04; 95% CI, 0.70–1.55; p=0.86	OS: - All population: 81 vs. 71 mo (HR, 0.78, 95% CI, 0.66–0.93, p=0.006) - Metastatic subgroup: 60 vs 45 mo (HR: 0.76, 95% CI 0.62–0.92, p=0.005) FFS: 37 vs 20 mo (HR: 0.61, 95% CI, 0.53–0.70, p<0.001)
Secondary Endpoints (experimental arm vs comparable arm)	bPFS: - All patients: 22.9 vs. 12.9 mo; HR, 0.67; 95% CI, 0.54-0.84, p<0.001 cPFS: - All patients: 22.9 vs. 15.3 mo; HR, 0.69; 95% CI, 0.55-0.87, p=0.002	- PSA level <0.2 mg/mL at 6 mo: 32% vs. 19.6%; p<0.001 - PSA level <0.2 ng/mL at 12 mo: 27.7% vs. 16.8%; p<0.001 - Time to CPRC: 20.2 vs. 11.7 mo; p<0.001 - Time to clinical progression: 33.0 vs. 19.8 mo; p<0.001	Prostate cancer–specific survival: - All populations: HR: 0.79; 95% CI, 0.65–0.96; p=0.019 - Metastatic subgroup: HR: 0.8; 95% CI, 0.65–0.99; p=0.033 - Nonmetastatic subgroup: HR 0.82; 95% CI, 0.48–1.40; p=0.475 - Time to first skeletal related event: HR: 0.60; 95% CI, 0.48–0.74; p=0.001
Adverse Events (experimental arm vs comparable arm)	-	- Grade 3-5: 29.4% (115/390)	- Grade 3-5: 52%/32% (288/399)

6.2 ABIRATERONE ACETATE + PREDNISONE

Roughly 2 years after chemohormonal therapy was established as the new standard therapy for patients with mHSPC, several new trials involving the use of novel hormone based therapies in combination with ADT emerged, being one of the most remarkable, the abiraterone acetate plus prednisone. AA is a selective irreversible inhibitor of the key enzyme CYP17A1, critical in androgens biosynthesis (Figure 1), was approved initially for patients with mCRPC. Thereafter, the LATITUDE (29) trial and, once more, the STAMPEDE (14) trial (arm G) investigated and reported the first conclusions, leading to the approval of abiraterone acetate as a first-line treatment regarding mHSPC (28).

The LATITUDE trial was a multinational, randomized, double-blind phase III trial that aimed to compare AA plus prednisone with ADT vs double placebo and ADT only in men with mHSPC. High risk definition on this trial was slightly different compared to previously docetaxel trials. Patients had to have de novo metastatic disease and were required to have at least two of the following features: a Gleason score ≥ 8, three or more bone metastases, and/or visceral

metastases, and, in addition, they could not have received previous chemotherapy, radiation, or any type of surgery for metastatic PCa other than for palliative intent. 1199 patients, who met the key requirements, were randomly assigned to receive ADT + AA (1000 mg per day) + Prednisone (5 mg per day) vs ADT plus placebo, in a 1:1 ratio. Stratification was achieved according to the ECOG performance-status (0-1 vs 2) and presence or non-presence of assessable visceral disease. Primary endpoints were OS and radiographic progression-free survival (rPFS). Secondary ones were the next SRE, time to progression with respect to PSA level, time to the next therapy for PCa, time to beginning of chemotherapy, and time to pain progression (29).

The first interim analysis had a median follow-up of 30,4 months AND showed a 17% OS at three years benefit when comparing AA group vs placebo group (66% vs 49%). Rate of death from any possible cause was 28% in AA against 39% in placebo. Relative risk of death was 38% lower in AA group than in placebo one (HR: 0.62, 95% CI: 0.51–0.76, p<0.0001). Concerning rPFS, median was 33 months in AA group vs 14,8 months in the placebo group (HR: 0.47; 95% CI, 0.39 - 0.55; p<0.001). Secondary endpoints, mentioned previously, also showed a clear superiority when using AA therapy. It is also worth mentioning that grade 3 or 4 AE were reported in 63% of all patients that used AA vs 48% in patients that used only ADT plus placebo. However, severe AE were similar across both groups. (29)

Finally, a long term analysis reported in April 2019 with a follow-up analysis of 51,8 months. OS kept being longer in the AA plus prednisone group vs the placebo group, 53.3 months vs 36.5 months (HR: 0.66, 95% CI 0,56−0,78, p<0,0001). A new subgroup analysis also displayed improvement in OS across most subgroups, apart from the one with patients with low volume disease defined by the CHAARTED criteria, such as the ones with ECOG performance-status of 2 and with patients with a Gleason score inferior than 8. Once more, consistent with the first analysis, all secondary endpoints were significantly improved in patients that received AA. Grade 3-4 AE were reported at a similar rate as before (68% in AA group vs 50% in placebo group). (13)

The multi-arm STAMPEDE trial (arm G) compared a group of patients that received 1000 mg daily of AA plus 5 mg daily of prednisone with ADT against the arm A, previously mentioned, which received ADT alone. The main objective was to assess its role in men with metastatic disease, N1 disease, and high-risk localized disease (N0M0). Stratification was based on age (<70 years vs ≥70 years), the presence or non-presence of metastases, if prostate radiotherapy was planned or not, nodal involvement, World Health Organization (WHO) performance-status (0 vs 1-2), type of ADT and if there was or not regular, long-term use of any nonsteroidal anti-inflammatory or aspirin. (14)

Of the 1917 patients enrolled, 52% had metastatic disease, 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, nonmetastatic

disease. The primary endpoint measured was OS. Secondary one was FFS. Median follow-up was 40 months, where the data suggested a strong benefit for the group with AA + prednisone with a 3-year survival of 83% vs 76% in the ADT-alone group (HR: 0,63, 95% CI 0,52-0,76, p<0,001). FFS also shown clear benefits in the group with AA + prednisone, with a 3-years FFS of 75% for the first group against 45% in the ADT alone group (HR: 0,29, 95% CI 0,25-0,34, p<0,001). Also, all sub-groups, specially the metastatic one (OS – HR: 0.61 95% CI 0.49–0.75; FFS – HR: 0.31 95% CI, 0.26–0.37), revealed benefit by using AA + prednisone. Regarding AE, grade 3 to 5 occurred in 47% of the patients in the arm G group (with only nine grade 5 events) and in 33% of the patients in the ADT-alone group (with three grade 5 events).Compared with docetaxel, AA was better tolerated. (14)

A resumed comparison with the most significant characteristics and results from these trials is shown below in Table 2.

Table 2. Selected Completed Clinical Trials Investigating Abiraterone Acetate in mHSPC.

Study characteristics	LATITUDE – POST-HOC (13)	STAMPEDE ARM-G (14)
Treatments used	ADT + AA 1000 mg daily + prednisone 5 mg daily vs ADT	ADT + AA 1000 mg daily + prednisone 5 mg daily vs ADT
Eligibility Criteria	- *de novo* mHSPC - 2 of 3: Gleason ≥8, >3 bone metastases, and/or visceral metastases - No prior chemotherapy/local treatment - ECOG 0-2	- Newly diagnosed mHSPC or node positive or high risk locally advanced (with ≥2 of T3/4, Gleason score of 8–10, PSA ≥40 ng/mL) or disease previously locally treated now relapsing
Patients (n; experimental arm/comparable arm)	1199 (597/602)	1917 (960/957)
Disease characteristics	79.6% with HVD	- 52% metastatic - 20% node positive - 28% node negative
Previous treatment allowance	Up to 3 months of ADT; single course of palliative radiotherapy or surgical therapy for the symptoms of the metastatic disease	Up to 3 months of ADT
Primary Endpoints (experimental arm vs comparable arm)	OS: - All population: 53.3 vs 36.5 mo (HR: 0.66, 95% CI 0,56−0,78, p<0,0001)	OS at 3-years: 83% vs 76% (HR 0.63; 95% CI, 0.52–0.76; p<0.001) - Nonmetastatic subgroup: (HR 0.75; 95% CI, 0.48–1.18)

	- rPFS: 33 vs 14.8 mo (HR: 0.47; 95% CI, 0.39 -0.55; p<0.001) Time to pain progression: 47.4 vs 16.6 mo (HR: 0.72, 95% CI, 0,61-0.86, p=0.00024) SRE: NR vs NR (HR: 0.75, 95% CI, 0,60-0.95, p=0.0181) Beginning hemotherapy: NR vs 57.6 mo (HR: 0.51, 95% CI, 0,41-0.63, p<0.0001) Time to next PCa therapy: 54.9 vs 21.2 mo (HR: 0.45, 95% CI, 0,38-0.53, p<0.0001) PSA progression: 33.3 vs 7.4 mo (HR: 0.31, 95% CI, 0,27-0.36, p<0.0001)	- Metastatic subgroup: HR 0.61; 95% CI, 0.49–0.75
Secondary Endpoints (experimental arm vs comparable arm)		FFS at 3-years: 75% vs 45% (HR: 0.29, 95% CI, 0.25-0.34, p<0.001)
Adverse Events (experimental Arm vs comparable arm)	Grade 3-4: 68% vs 50%	Grade 3-5: 47% vs 33%

6.3 ENZALUTAMIDE

In 2019, new trials about a new-generation antiandrogen agent emerged in order to approve and increase the mHSPC treatment sphere. Enzalutamide (formerly known as MDV3100) is a target androgen-receptor inhibitor that inhibits androgen-receptor translocation to the cell nucleus, recruitment of androgen-receptor cofactors, and androgen-receptor binding to DNA (Figure 1). It also has a larger affinity for the receptor, promotes tumor shrinkage and has no known (by data) agonistic effects. In a previous phase III study, enzalutamide, in men with mCRPC who had previously received docetaxel, showed a prolonged OS and PFS (30-32).

The first one, a multinational, randomized, double-blind, phase III trial named ARCHES evaluated 1150 patients with prostate adenocarcinoma confirmed pathologically with radiologic evidence of metastasis and an ECOG performance-status score of 0 or 1 and up to six cycles of prior docetaxel chemotherapy or ADT alone were allowed (17.9% of all patients), but patients could not experience disease progression while taking these treatments before randomization. Randomization was achieved on a 1:1 ratio with a group receiving 160mg/day of enzalutamide plus ADT, whereas the control group received placebo plus ADT. Stratification included disease volume (high vs low) and prior presence, or not, of docetaxel therapy for PCa (0 cycles of treatment vs 1-5 cycles vs 6 cycles). 63,2% of all had HVD (defined by CHAARTED criteria). In this case, the primary endpoint was rPFS. Secondary endpoints were: OS, time to PSA evolution, time to initiation of other antineoplastic therapy, PSA undetectable rate, time to

deterioration of urinary symptoms, objective response rate, time to first symptomatic skeletal event, time to castration resistance PCa, patient-reported outcomes (PRO), time to worsening of quality of life (QoL), and time to pain progression (15).

Median follow-up was 14.4 months. Being this short, the median rPFS was NR in the enzalutamide plus ADT compared with 19 months in the placebo plus ADT group (HR: 0.39, 95% CI 0.30-0.50, p<0.001). Tough, enzalutamide plus ADT showed a significant reduce risk of radiographic disease progression/death vs placebo plus ADT (HR: 0.39, 95% CI, 0.30-0.50; p<0.001). Across all subgroups, the effect of this treatment was consistent, such as the HVD vs LVD subgroups and in patients that received docetaxel. The secondary ones that showed a clear benefit of the enzalutamide plus ADT treatment were: time to PSA evolution, time to initiation of new antineoplastic therapy, PSA undetectable rate, and objective response rate (ORR). Prevention of SRE and castration resistance also were reduced with enzalutamide plus ADT. QoL was not unfavorably affected with the addition of enzalutamide, based on the Functional Assessment of Cancer Therapy – Prostate (FACT-P) score and time to pain progression. Unfortunately, OS data were immature to provide consistent and reliable conclusions. AE-wise, no unexpected AEs occurred, being the rates similar in both arms, with 24,3% of patients receiving enzalutamide reporting grade 3 AE against 25,6% of patients in the placebo arm (15).

Simultaneously, the open-label, phase III trial ENZAMET randomized 1125 eligible patients with mHSCP to receive 160mg daily of enzalutamide plus ADR, or another nonsteroidal antiandrogen (such as, bicalutamide, flutamide, or nilutamide) with ADT. These patients had to have a score of 2 or less on the ECOG performance-status scale, could not have received testosterone suppression therapy within the past 12 months, but early docetaxel treatment was approved up to two cycles before randomization. Stratification was as follows: the volume of disease (high vs low, defined by CHAARTED criteria), planned early use of docetaxel (yes vs no), planned use of bone antiresorptive therapy (yes vs no) and, finally, the score on the Adult Comorbidity Evaluation 27 (ACE-27) (0-1 vs 2-3) (33). Primary endpoint was OS while secondary endpoints were PSA PFS, clinical progression, any cause of death and PSA progression. HVD was present in 52% of all patients and 45% had early docetaxel treatment planned. (16)

The early first interim analysis after a median follow-up 34 months observed a clear survival advantage in the enzalutamide group against those being treated with other nonsteroidal antiandrogens (HR: 0.67, 95% CI: 0.52–0.86, p=0.0002). Even though median OS was not yet reached in both arms, OS in 3 years' time, is estimated to be 80% in the enzalutamide group vs 72% in the nonsteroidal antiandrogens one. Even clearer was the effect of enzalutamide on PSA PFS and clinical progression. For the first, at 3 years, the rate of

event-free was 67% for the enzalutamide group vs 37% in the standard-of-care (SOC) group (HR: 0.39; 95% CI, 0.33-0.47; p<0.001). Regarding clinical progression, the rate of event-free survival was 68% vs 41% respectively (HR: 0.40; 95% CI, 0.33-0.49; p<0.001). Between subgroups, OS with enzalutamide had a less significant impact in the ones with bone antiresorptive therapy, HVD and planned early docetaxel treatment. It is worth stating that the smaller amount of deaths anticipated might have had a crucial influence in these results and further analysis soon is desirable, according to the authors. Nevertheless, secondary endpoints results were consistent across all subgroups, particularly the clinical progression parameter. Treatment duration was meaningfully longer for enzalutamide compared with SOC group, with 62% vs 34% still on treatment 3 years later. This numbers are particularly important regarding AE. Even though AE events were higher in the enzalutamide group, when adjusted for person-years on treatment, the rate was similar. (16)

It is worth pointing out three key differences between the ARCHES and ENZIMET trials. Firstly, whereas ARCHES evaluated rPFS as the primary endpoint, ENZAMET opted for OS. Secondly, the comparison group was significantly different between both, being placebo in the first and nonsteroidal antiandrogen in the second. Thirdly, while both trials allowed docetaxel treatment, ARCHES only allowed treatment with enzalutamide to be administered after the conclusion of docetaxel, whereas ENZAMET allowed concurrent early docetaxel use. (16)

A resumed comparison with the most significant characteristics and results from these trials is shown below in Table 3.

Table 3. Selected Completed Clinical Trials Investigating Enzalutamide in mHSPC

Study characteristics	ARCHES (15)	ENZAMET (16)
Treatments used	Enzalutamide 160 mg daily + ADT vs Placebo + ADT	ADT + Enzalutamide 160 mg daily vs ADT + standard nonsteroidal antiandrogen (bicalutamide, nilutamide, flutamide)
Eligibility Criteria	- mHSPC - ECOG: 0-1	- mHSPC - ECOG 0–2 - Not received testosterone suppression therapy within the past 12 months
Patients (n; experimental arm/comparable arm)	1150 (574/576)	1125 (563/562)
Disease characteristics	63.2% with HVD	52.5% with HVD

Previous treatment allowance	Up to 6 cycles of prior docetaxel or ADT (17.9%) without disease progression	Up to 2 cycles of early docetaxel
Primary Endpoints (experimental arm vs comparable arm)	- rPFS: NR vs. 19 mo (HR: 0.39, 95% CI 0.30-0.50, p<0.001) - Radiographic disease progression: 13.8% vs. 32.6% (HR: 0.39, 95% CI, 0.30-0.50; p<0.001)	- OS estimation at 3 years: 80% vs 72% (HR: 0.67; 95% CI, 0.52-0.86, p=0.002)
Secondary Endpoints (experimental arm vs comparable arm)	- Time to PSA progression: NR vs NR (HR:0.19, 95% CI, 0.13-0.26, p<0.001) - PSA undetectable rate: 68.1% vs 17.6% (p<0.001) - Time to new antineoplastic treatment: 30.2 mo vs NR (HR:0.28, 95% CI, 0.20-0.40, p<0.001) - ORR: 83.1% vs 63.7% (p<0.001 - OS: NR vs NR (HR: 0.81, 95% 0.53-1.25, p<0.3361)	- PSA PFS at 3 years: 67% vs. 37%; (HR: 0.39 95% CI, 0.33-0.47; p<0.001) - Clinical PFS: event-free at 3 years: 68% vs. 41% (HR, 0.40 95% CI, 0.33-0.49; p<0.001)
Adverse Events (experimental arm vs comparable arm)	Grade 3-5: 24.3% vs 25.6%	Grade 1: 7% vs 14% Grade 2: 36% vs 41% Grade 3: 49% vs 35% Grade 4: 7% vs 7% Grade 5: 1% vs 1%

6.4 APALUTAMIDE

Apalutamide (formerly known as ARN-509), like enzalutamide, is a novel treatment for PCa. Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen receptor translocation, androgen receptor–mediated transcription, and DNA binding (Figure 1) (34, 35).

In the beginning of 2018, the SPARTAN trial firstly presented apalutamide potential in patients with nonmetastatic mCRPC, by demonstrating a significant improvement in metastasis-free survival and time to symptomatic progression (35). A few months later, a randomized, double-blind, placebo-controlled, phase III study, randomized 1052 patients with mHSPC, to receive 240mg daily of apalutamide or placebo, in addition to continuous ADT. The TITAN trial only allowed patients who had a documented adenocarcinoma of the prostate with distant metastatic disease of at least one lesion on bone scanning, containing, or not, visceral or lymph-node involvement, ECOG performance-status of 0 or 1, were castration sensitive,

could only have been previously treated with docetaxel (up to 6 cycles). Moreover, they could only have had received ADT for no more than 6 months, one course of radiation or surgical treatment for metastasis-related symptoms and other type of therapy for localized disease, such as radiation therapy or prostatectomy, had to be completed at least one year before randomization. Stratification was according to Gleason score when PCa diagnostic was performed (7≤ or >7), geographic region and if there was or not a previous treatment with docetaxel (10.7% of all). Primary endpoints were OS and PFS. Secondary endpoints were time to cytotoxic chemotherapy, time to chronic opioid use, time to SRE, and time to pain progression as assessed by the Brief Pain Inventory–Short Form (BPI-SF). Other relevant secondary objective was to analyze the data between subgroups with a HVD (62,7%) vs LVD (defined by the CHAARTED criteria). Exploratory end points defined also by the authors included second PFS, time to PSA progression and time to symptomatic local progression. (17)

At the first interim analysis, with a median follow-up of 22.7 months, at 24 months, rPFS was 68,2% in the apalutamide groups vs 47,5% in the placebo group (HR: 0.48, 95% CI 0.39–0.60, p<0.001) while OS was 82,4% vs 73,5%, respectively (HR: 0.67; 95% CI, 0.51 to 0.89, p=0.005), with consistent beneficial results across all subgroups, especially the volume disease one. Concerning secondary endpoints, time to cytotoxic chemotherapy, time to PSA progression, duration of second PFS and patients reaching undetectable PSA levels all presented strong results in the apalutamide group (17, 25). Grade 3-4 AEs (42.2% vs 40.8%, respectively) and serious AE (19.8% vs 20.3% respectively) did not present a substantial difference between both groups. (17)

A resumed comparison with the most significant characteristics and results from this trial is shown below in Table 4.

Table 4. Selected Completed Clinical Trials Investigating Apalutamide in mHSPC

Study characteristics	**TITAN (17)**
Treatments used	ADT + Apalutamide vs ADT + placebo
Eligibility Criteria	- mHSPC with at least one lesion on bone scan, containing, or not, visceral or lymph-node involvement - ECOG 0–1 - Castration sensitive
Patients (n; experimental arm/comparable arm)	1052 (525/527)
Disease characteristics	62.5% with HVD
Previous treatment allowance	ADT for no more than 6 months;

	Single course of palliative radiotherapy or surgical therapy for the symptoms of the metastatic disease or other therapy for localized disease (10.7%)
Primary Endpoints (experimental arm vs comparable arm)	- rPFS at 24 mo: 68.2% vs 47.5%,(HR: 0.48, 95% CI 0.39–0.60, p<0.001) - OS at 24 mo: (HR: 0.67; 95% CI, 0.51 to 0.89, p=0.005)
Secondary Endpoints (experimental arm vs comparable arm)	- Time to cytotoxic chemotherapy: not estimated (NE) vs NE (HR: 0.39, 95% CI, 0.27–0.56, p<0.001) - Time to pain progression: NE vs NE (HR: 0.83, 95% CI, 0.65–1.06, p=0.12) - Time to skeletal-related events: NE vs NE (HR:0.8, 95% CI, 0.56-1.15) - Time to chronic opioid use: NE vs NE (HR: 0.77, 95% CI, 0.54-1.11)
Adverse Events (experimental arm vs comparable arm)	Grade 3-4: 42.2% vs 40.8%

6.5 DATA COMPARISON

With these four systemic treatment regimens showing benefit in the mHSPC condition, and after the approval from major health agencies worldwide, clinicians treating these patients are presented, on a daily basis, with the dilemma of choosing the best treatment for each patient. Unfortunately, so far, no prospective trial has randomized patients to directly compare efficiency and tolerability between them. However, trials like the STAMPEDE, where multiple arms were studied together, indirect comparisons between a few of the available treatments were made possible. With a 4 years median follow-up, a post hoc analysis of the STAMPEDE trial (36) only showed benefit in FFS in the AA group, comparatively with the docetaxel group. All other endpoints, such as OS, PCa-specific survival, metastasis-free survival and symptomatic SRE, did not show any statistically advantage. Another meta-analysis, which aimed to compare indirectly ADT + docetaxel vs ADT + AA (37) across the GETUG-AFU15, CHAARTED, LATITUDE, and docetaxel and AA arms of the STAMPEDE, with a total of 6067 patients, did not demonstrate a statistically significant difference in OS between both therapy modalities (HR 0.84, 95% CI 0.67–1.06). Though, using a Bayesian approach for network meta-analysis (38) suggested that there is a high likelihood that AA + ADT is the preferred approach. The first meta-analysis to perform an indirect comparison between all 4 new treatment approaches was released in mid-2019. (39) Out of all 4, OS did not appear to have a significant difference between one-another. For LVD, only enzalutamide demonstrated improved OS compared to ADT and superior to docetaxel. For HVD, similarly to primary OS, no treatment was better than another. PFS-wise, enzalutamide and AA were substantially better than docetaxel and apalutamide. Lastly, one late 2020 meta-analysis also compared all

4 treatments. (40) With a total of 10 randomized controlled trials, 16 full articles and 11174 patients included, no treatment showed OS superiority against other of the 4. Regarding FFS, ADT + AA and ADT + Enzalutamide, once again, showed a benefit compared to the ADT + docetaxel regimen. Concerning subgroup analysis, in patients with HVD, ADT + AA also seemed to be the best therapy in terms of OS and FFS. For LVD, ADT + AA was preferred when talking about FFS but, in terms of OS, ADT + enzalutamide was considered preferable.

6.6 DISEASE VOLUME

Disease volume has gained a huge importance throughout the years by being a key predictive factor in the selection criteria for treatment. The two major criteria defined and subsequently most used to distinguish between HVD and LVD (Figure 2) were from the LATITUDE (29) and CHAARTED (12) trials, being this last one the most applicable. In patients with HVD, all these newer four treatment options statistically reasonable.

Regarding docetaxel, because of the early results, previously displayed, where no positive effect occurred in the majority of subgroups with LVD, many clinicians have been reserving these treatment option only for patients with HVD as defined by the CHAARTED criteria. However, the most recent updated analysis from the STAMPEDE trial (41), also previously mentioned, shifted and reopened the debate on whether docetaxel can have a word in treating patients with LVD mHSPC.

About AA + ADT on the LATITUDE trial post-hoc analysis, OS did show a significant advantage in the HVD group (HR: 0.62, 95% CI, 0.52−0.74; p<0.0001), while the LVD did not reach statistical significance (HR 0.72, 95% CI 0.47−1.10, p=0.12). Nevertheless, rPFS had a benefit in both groups (HR: 0.46, 95% CI 0.39−0.54, p<0.0001; HR: 0.59, 95% CI 0.40−0.85, p=0.0048; respectively). But the caveat here was later explained, where the relatively small number of LVD patients might have influenced the results. A post-hoc analysis of the STAMPEDE arm C also aimed to evaluate the influence of volume disease (42). The results were clear throughout all endpoints, like OS or FFS and even when using the 2 different criteria for HVD/LVD usually used by clinicians the results were consistent. To sum up, the available evidence suggests that AA is beneficial regardless of disease volume.

In the 2 trials that reported to the use of enzalutamide, the balance between HVD/LVD patients selected was more considered, which, thereafter, providing more reliable results. In the ENZAMET, efficacy of enzalutamide on OS was smaller among the subgroup with HVD, though still statistically relevant, (16) suggesting that enzalutamide reveals efficacy in both HVD and LVD. Apalutamide, on the same hand, did demonstrate a benefit in all subgroups

analyzed comparing HVD vs LVD (HR: 0.68, 95% CI, 0.50–0.92; HR: 0.67, 95% CI 0.34–1.32; respectively).

Stratifying treatment choice by disease volume has been the biggest challenge in recent years for clinicians and one the most disputed among the scientific community studying new mHSPC treatment approaches. The report from the Advanced Prostate Cancer Consensus Conference 2019, published in 2019, stated that more than 85% of the panel voted for some form of additional treatment together with ADT in de novo metastatic setting, regardless of disease volume (43). Other relevant conclusion occurred when there was a preference between the panel for antiandrogens in LVD.

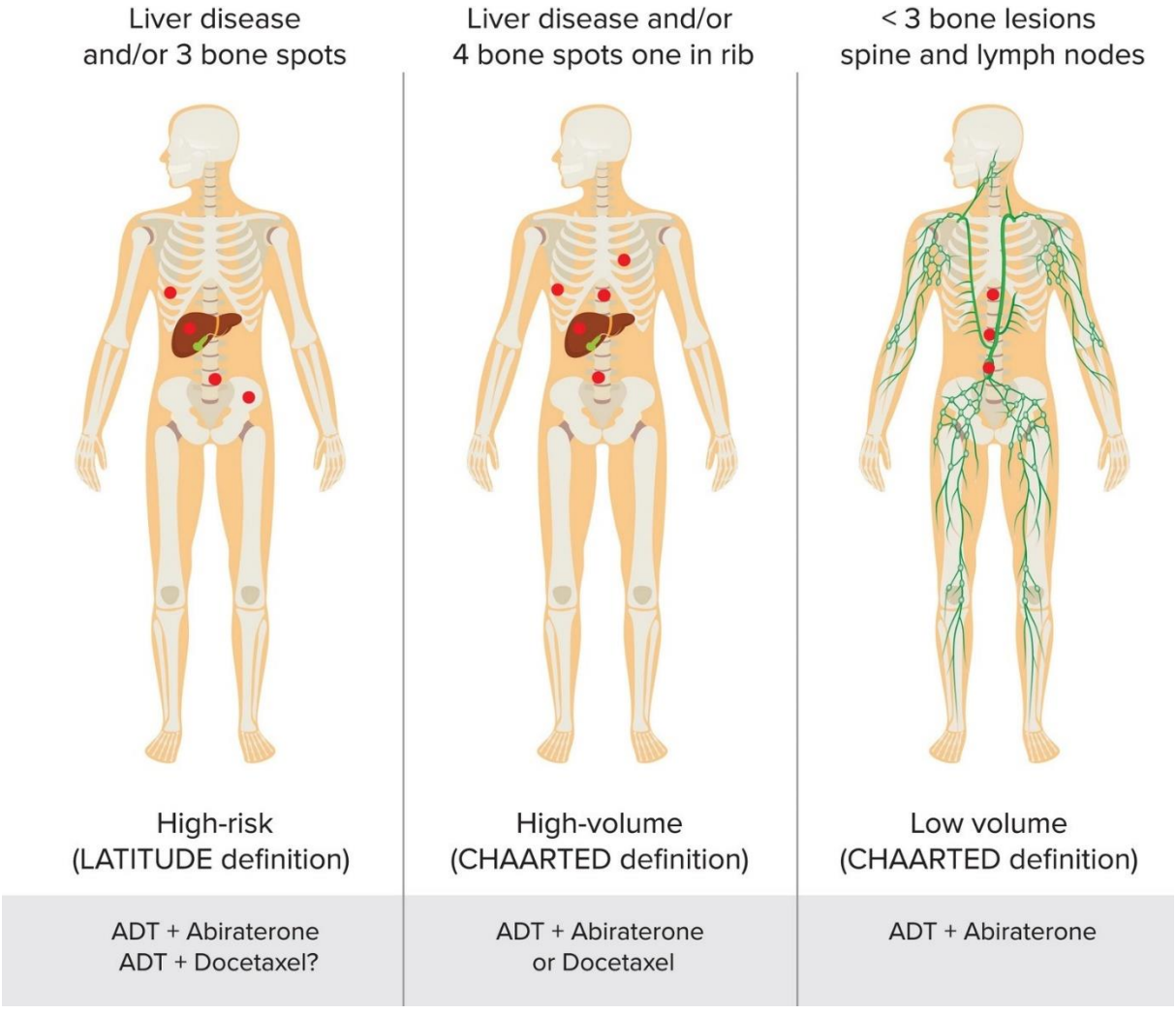

Figure 2. Clinical presentation of metastatic hormone-sensitive prostate cancer with the CHAATERD and LATITUDE criteria for high and low volume disease. ADT - androgen deprivation therapy. Adapted from (44)

6.7 COST

Considering the broad type of health systems existing worldwide, a pharmacoeconomic evaluation is always worth mentioning, especially when several treatment options are considered valid for the same type of illness and do not have substantial differences in primordial outcomes, such as OS or PFS. Pharmacoeconomics evaluates the cost/benefit of drug therapy under these following aspects: the cost of the treatment to the health system, how much it improves disease prognoses, the demand and supply of the treatment, and the budget (45). The two main concepts to consider are the quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER). (46, 47).

The first analysis released in 2017, only compared ADT + docetaxel vs ADT alone. In the metastatic disease scenario, there was an increase of 0.53 QALY with the addition of docetaxel to ADT. In patients with HVD (using CHAARTED criteria) the increase in QALY was more significant, 0.7. The conclusion of this trial was that the addition of docetaxel to ADT in PCa is only a cost-effective measure for patients with HVD. (46)

But being docetaxel an “old” drug, currently can be produced as a generic, being therefore, an affordable option, while all the other 3 treatments, as being new oral agents, their cost-effectiveness might not justify the small difference in efficiency for same patients/health systems/insurance companies. Very soon AA will also be a generic drug In 2018, was consequently released a trial that compared the cost-effectiveness of docetaxel or AA + ADT in patients with mHSPC, measuring also the QALY and costs from a US private payer. When compared with ADT alone, either treatment with docetaxel or AA improved QALYs with a higher cost. Docetaxel + ADT represented the highest value with an ICER of $4.723/QALY, whereas, AA had a ICER of $295.212/QALY, which was considered not favorable, compared to ADT alone (18). There is yet to come an analysis with enzalutamide and apalutamide which will be crucial to help clinicians choosing the best treatment regimen for their patients in many of the countries.

6.8 ADVERSE EVENTS

QoL and the side effects of chemotherapy is another major concern for cancer patients. With a median OS of roughly 4 years from the time of diagnosis of mHSPC, it is imperative to find the balance between efficacy of treatment with any treatment-related adverse events, in particular long-lasting effects which may compromise the patient’s QoL.

Docetaxel, as an intravenous chemotherapy, has a timeframe for administration up to 18 weeks (every 3 weeks, up to 6 cycles) which permits that any reversible adverse effects and time away from social and professional commitments are condensed in time. In contrast,

antiandrogens are given up to the point of progression or intolerability. Moreover, the overall cost is significantly lower. However, docetaxel is hard to tolerate for patients with advanced age, poor performance status or coexisting illnesses and need to be considered “fit for chemotherapy” (23-25).

Generally, the new antiandrogens are extremely better tolerated, compared to docetaxel, with few high-grade AEs. The STAMPEDE investigators compared QoL scores of the trials where patients were recruited to receive docetaxel and AA. Over 2 years, the average global QoL was higher in patients randomized to AA, with a cross-sectional analysis showing clinical superior QoL in the AA group at 3–6 months (48). In both the ARCHES and TITAN trials, which studied enzalutamide and apalutamide, respectively, QoL was assessed by the FACT-P score (15, 16). The QoL scores did not differ between the new treatment groups and control ones. Even though this good tolerability is broad across the oral antiandrogens, a few AE can exist in each specific treatment and require close attention to prevent not expected outcomes (23-25).

Phase I/II trials about enzalutamide associated an increase episode of seizures when taking these medication (49), which prevented phase III trials to include patients with this medical history or brain metastatic lesions. Moreover, the incidence of grade 3 hypertension doubled in the enzalutamide arm compared with ADT alone. Apart from these specific AE, docetaxel and AA required the addition of steroids so patients with poorly controlled diabetes mellitus may not be good candidates for these treatments’ regimens. Cardiac, hepatic and vascular disorders were also more common for patients treated with AA vs ADT alone, so patients with a significant cardiac background should want to avoid AA in the first-line setting (41).

7. CONCLUSION

The SOC, for the past several decades, for mHSPC has changed substantially and continues to progress with the advent of new systemic agents. From a stagnation period over decades where ADT alone were considered the gold treatment approach, this is no longer the case. The transition of multiple systemic treatments, previously used in the mCRPC setting, into the mHSPC environment is as exciting as challenging. Apart from the obvious benefits of improving OS, among other secondary and relevant clinical outcomes, which, with the increase focus on a patient centered medicine, gained even more relevance in the clinical practice, the use of multiple antiandrogen agents in the mHSPC setting also tests the paradigm of splitting PCa treatment into the castrate-resistant and castrate-sensitive phases.

The better understanding of the heterogeneity of the mHSPC disease, it is associated biomarkers and consequentially appropriate treatment sequencing has been leading to an increasing focus on biologically based disease taxonomy. Multiple trials in the mHSPC environment, are enrolling as of writing, which will continue to clarify the role and sequence of administration for each of these agents.

Hence the importance of selecting the appropriate treatment based on individual comorbidity profile, economical background and preference cannot be over-emphasized. Unavoidably, physician experience and preference while prescribing these medications in the mHSPC setting will influence individual prescribing patterns (23-25).

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I would like to finish with a sentence presented by Prof. Dr. Arnaldo Figueiredo in the Urology class regarding the exact same theme in which I wrote this thesis.

"Is cure necessary in those in whom it may be possible? Is cure possible in those in whom it may be necessary?" (50)

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