FUTURE ONCOLOGY
2025, VOL. 21, NO. 8, 991–1003
https://doi.org/10.1080/14796694.2025.2468569

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PERSPECTIVE

Beyond the status quo: when disease volume and metastatic timing are not enough to personalize treatment in mHSPC

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ABSTRACT

This review explores the complexities of treatment intensification in metastatic hormone-sensitive prostate cancer (mHSPC), emphasizing the limitations of using disease volume and metastatic timing as sole prognostic factors. Current algorithms focus on clinical factors like ECOG, comorbidities, and patient preferences, yet lack biomarkers for more individualized therapy. By examining prognostic indicators – clinical, analytical, pathological, molecular, and imaging – this article highlights the importance of a personalized approach. Multimodal strategies and predictive biomarkers are proposed to optimize therapy selection between doublet and triplet regimens, ultimately improving patient outcomes. Future trials incorporating emerging biomarkers may provide the basis for precision treatment in mHSPC, shifting management beyond conventional classifications.

ARTICLE HISTORY
Received 8 January 2025
Accepted 14 February 2025

KEYWORDS
Metastatic hormone sensitive prostate cancer; prognosis; disease volume; metachronous; synchronous; personalized treatment; treatment intensification

1. Introduction

Prostate cancer (PC) stands as the second most common cancer among men worldwide, significantly contributing to cancer-related illness and mortality. In 2024, an estimated 299,010 new cases are expected, accounting for 14.9% of all new cancer diagnoses, with an anticipated 35,250 deaths, or 5.8% of total cancer-related fatalities. The 5-year relative survival rate from 2014 to 2020 is 97.5% [1,2]. In developed countries, most cases are identified when the cancer is still localized to the prostate, largely due to the widespread use of prostate-specific antigen (PSA) screening. Its diagnosis and presentation can be influenced by a variety of factors including socio-demographic, geographic, economic, and biological aspects [3]. Metastatic PC encompasses various disease states, categorized by their response to androgen deprivation therapy. These include metastatic hormone-sensitive prostate cancer (mHSPC) and castration-resistant prostate cancer (mCRPC) [4].

This perspective article aims to examine the ongoing debate on treatment intensification in mHSPC, specifically focusing on determining the optimal therapeutic strategy between doublet and triplet regimens. As the treatment landscape for mHSPC evolves with new combination therapies, it is essential to understand when and how to intensify treatment based on factors beyond disease volume. To address this, a panel of experts specializing in genitourinary malignancies reviewed the key prognostic factors that inform treatment decisions for mHSPC patients. They also responded to a series of consensus questions, with the goal of providing guidance on personalizing therapy and improving clinical outcomes for this diverse patient population.

2. mHSPC: prognosis classification

The status of mHSPC encompasses various profiles, each with distinct prognoses based on the timing and extent of metastasis. In recent years, the introduction of new treatment options has significantly transformed management strategies, underscoring the importance of a multidisciplinary team in tailoring care to each patient's journey. This collaborative approach is crucial for creating personalized treatment plans that not only aim to prolong survival and maintain quality of life but also reduce the burden associated with existing therapies [4].

2.1. Disease volume and timing of metastatic disease as key, but not sufficient prognostic factors for mHSPC to tailor treatment

Understanding the complex landscape of prognostic factors influencing disease progression is crucial for selecting optimal

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Article highlights

Introduction
- Metastatic hormone sensitive prostate cancer (mHSPC) treatment lacks universally optimal strategies; individualized approaches are essential.
- Conventional classification systems using disease volume and metastatic timing are insufficient for tailoring therapy.
- A multidisciplinary perspective and emerging biomarkers are critical for advancing personalized care.

Prognosis classification in mHSPC
- Prognostic groups vary by metastatic timing and disease volume: good, intermediate, and poor outcomes are defined based on these factors.
- High-volume, de novo metastatic cases show the poorest survival and require intensive treatment strategies.
- Low-volume cases benefit from tailored doublet therapies, sparing toxicity from triplet regimens.

Key prognostic factors for treatment decisions
- Clinical: Age, comorbidities, and functional status guide the choice between doublet and triplet therapies.
- Analytical: High lactate dehydrogenase and alkaline phosphatase, low hemoglobin, and PSA kinetics are prognostic of outcomes.
- Pathological: High Gleason scores and molecular alterations like TP53 mutations correlate with aggressiveness.
- Imaging: Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography (PSMA PET/CT) reveals disease extent beyond conventional imaging, influencing classification.

Emerging biomarkers and therapeutic strategies
- Advances in transcriptomic profiling and molecular imaging enhance prognostic accuracy.
- Poly (ADP-Ribose) Polymerase (PARP) inhibitors and PSMA-targeted therapies are promising additions for specific subgroups.
- Ongoing trials focus on integrating genomic classifiers and personalized treatment combinations.

Consensus insights on therapy optimization
- Doublet therapy is preferred for low-volume disease, while triplet therapy benefits high-volume cases.
- Radiotherapy is valuable for managing local tumor burden and symptomatic relief.
- PET-PSMA staging improves precision but requires careful application in treatment planning.

Future perspectives
- Biomarker-guided therapies hold potential for balancing treatment efficacy and burden.
- Real-world data and advanced clinical trial designs will shape the next generation of mHSPC management.

Conclusion
- Personalized approaches integrating clinical, pathological, analytical, and molecular factors are key to optimizing outcomes in mHSPC.
- Tailored strategies hold the promise of improving survival while reducing treatment-related burdens for diverse patient populations.

treatments and identifying patients suitable for therapy intensification. The primary goals are to identify clinical, imaging, and molecular factors linked to survival and treatment efficacy.

Prognosis assessment plays a key role in guiding treatment decisions for mHSPC patients. Typically, patients with metachronous metastases – those occurring after the initial localized prostate cancer diagnosis – have a better prognosis than those with synchronous metastases, which are present at diagnosis [5,6]. While CHAARTED criteria categorize both synchronous and metachronous high-volume disease similarly, clinical evidence indicates a prognostic distinction. Metachronous high-volume disease, despite fulfilling the high-volume definition, is associated with a more indolent disease course and improved outcomes, with median overall survival extending beyond that observed in synchronous high-volume disease (e.g., 48 months vs. 33 months, respectively). Clinical trials, such as CHAARTED and LATITUDE, highlighted the importance of these factors [5,6]. The CHAARTED criteria classify patients into high- or low-volume disease based on the extent of metastasis, while the LATITUDE criteria incorporate Gleason score as a high-risk factor. Both disease volume and the timing of metastasis are crucial prognostic factors, with significant differences in overall survival (OS) based on these variables. In the extended CHAARTED study, which included 790 mHSPC patients, the impact of disease volume on outcomes with androgen deprivation therapy (ADT) was examined. The results demonstrated that chemohormonal therapy significantly improved OS in patients with high-volume disease, but no survival benefit was observed in those with low-volume [7]. Similarly, Francini et al. studied 436 mHSPC patients to evaluate the effects of metastatic timing (post-local therapy vs. de novo) and disease volume on outcomes with ADT [8]. The study revealed that patients who received prior local therapy and had low-volume disease had a median OS of 92.4 months, compared to 43.2 months for those with de novo, high-volume disease. Patients with either prior local therapy and high-volume disease or de novo and low-volume disease had intermediate survival outcomes. This classification was strongly correlated with OS in mHSPC patients treated with ADT, demonstrating a significant trend across all groups ($p < 0.0001$). Based on these findings, three distinct prognostic groups for mHSPC patients treated with ADT were established, defined by the timing of metastatic disease occurrence (post-localized tumor vs. de novo) and disease volume (low vs. high):

2.1.1. Good prognosis

Metachronous low-volume disease: These patients have metastatic disease that occurred after initial treatment for a primary localized tumor and have a low volume of disease.

According to observational data, these patients exhibit a prolonged overall survival (median OS: 92.4 months) and a longer time to CRPC (median time to CRPC: 25.6 months) with ADT. While these findings highlight the natural history of the disease in this population, treatment decisions should be contextualized within the broader evidence base supporting therapy intensification in mHSPC.

2.1.2. Intermediate prognosis

Metachronous high-volume disease or synchronous low-volume disease: Primary localized tumor with high volume or de novo with Low volume: This group includes patients with either a high volume of disease that occurred after initial treatment for a primary localized tumor or a low volume of disease that presented de novo. This group of patients had a varied prognosis and might benefit from additional treatment strategies, such as the combination of ADT with chemotherapy or novel hormonal agents (NHA).

2.1.3. Poor prognosis: synchronous high-volume disease

Patients in this group present with high-volume metastatic disease at the time of initial diagnosis (de novo). They have the poorest prognosis, with a median OS of 43.2 months and a time to CRPC of 12.2 months, both significantly shorter

compared to the primary localized tumor with low volume group. Their risk of reduced survival and quicker progression to CRPC doubles that of the primary localized tumor with low volume cohort. These patients are likely less dependent on androgen signaling and may have a more aggressive disease phenotype. As a result, they might benefit substantially from the addition of chemotherapy to ADT, as demonstrated by improved survival rates in studies such as CHAARTED [6] or in the current state of the art the triple combination of ADT plus NHA plus chemotherapy (PEACE 1, ARASENS) [9,10].

The varying survival probabilities among the three prognostic groups in mHSPC underscore the importance of individualized treatment. For patients with de novo high-volume disease, it is hypothesized that the disease may be less reliant on testosterone, making the addition of chemotherapy on top of ADT + NHT a more effective treatment scheme. In contrast, chemotherapy appears to provide little benefit for patients with prior local therapy and low-volume disease. In many cases, both triple therapy and doublet therapy can be considered viable treatment options, though the use of doublet therapy with docetaxel is not well-supported. As a result, it is essential to look beyond disease volume and the timing of metastatic onset when making treatment decisions. This highlights a limitation in a recent algorithm (Figure 1) [11], which primarily considers factors like disease volume, ECOG status, comorbidities, drug interactions, and patient preferences to guide therapy. To better personalize treatment, incorporating biomarkers is essential to refine these recommendations and provide more tailored options for mHSPC patients.

2.2. Other key prognostic factors to be considered for more informed treatment decisions for patients with mHSPC

The selection of treatment for mHSPC remains complex due to the significant heterogeneity of the disease and the wide variation in patient characteristics. In clinical practice,

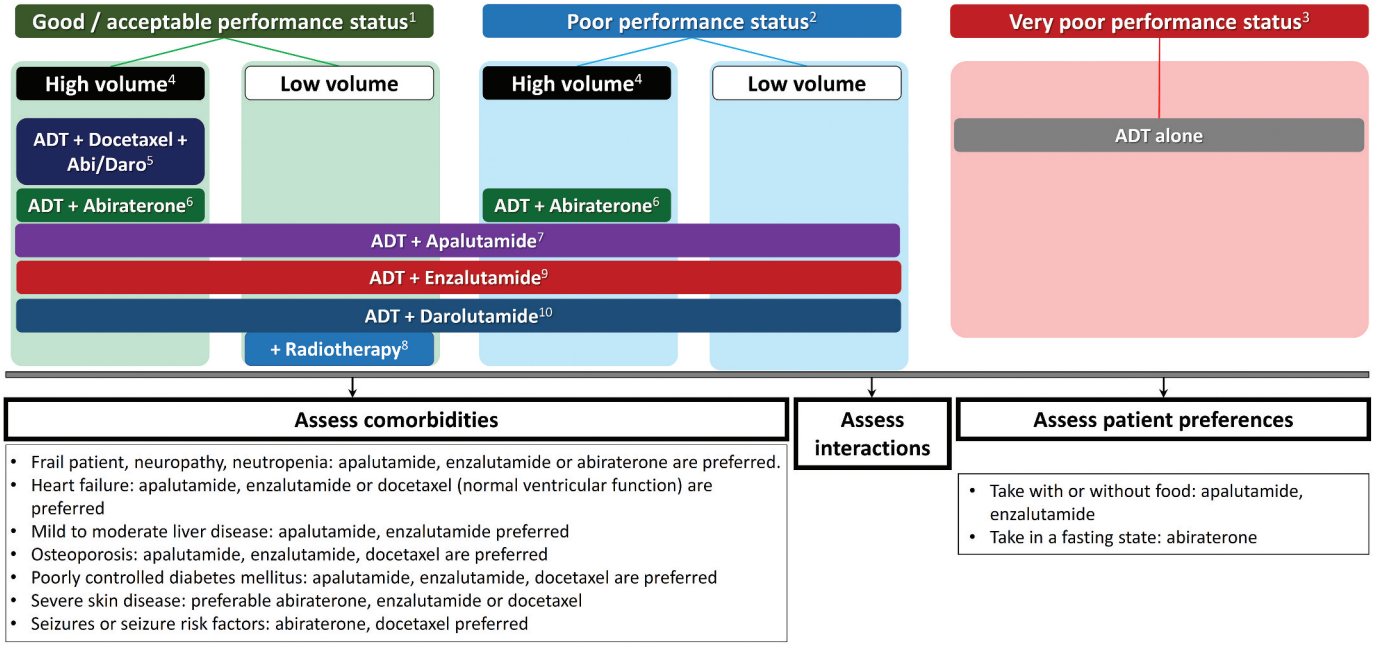

Figure 1. Algorithm with recommendations for additional treatment to ADT in mHSCP.

*mSCPH: metastatic hormone-sensitive prostate cancer; ADT: androgen deprivation therapy; Abi: Abiraterone; Daro: Darolutamide.

1. They are patients with the ability to tolerate docetaxel ("fit" patients). This criterion varied in the different studies. The CHAARTED study included patients with ECOG (Eastern Cooperative Oncology Group): 0–1, or 2 if impairment was due to cancer; the STAMPEDE study included patients with performance status 0–2 on the World Health Organization (WHO) scale; the GETUG-AFU 15 study included patients with a Karnofsky index ≥ 70%. Any of these criteria could indicate that the patient is a candidate for docetaxel.

2. Patients who are not candidates for docetaxel (eg: ECOG > 2 or 2 if impairment is not due to cancer; WHO performance status > 2 or Karnofsky index < 70%).

3. They are not candidate patients for docetaxel (fragile, poor medullary reserve, peripheral neuropathy) or new hormonal therapies.

4. 'High volume' disease is defined as the presence of visceral metastases, or four or more bone lesions with at least one of them outside the vertebral bodies and pelvis.

5. The most recent recommendations of the National Comprehensive Cancer Network (NCCN) recommend associating docetaxel with abiraterone or darolutamide in patients with high volume. In PEACE-1, the benefit of the triplet (TPA+DOCE+ABI) in OS is observed only in "'de novo'" and high-volume patients, while in ARASENS the benefit of the triplet (TPA+DOCE +DARO) is observed in both "'de novo'" patients as well as in patients after primary treatment. However, abiraterone is indicated only in combination with prednisone or prednisolone for the treatment of newly diagnosed high-risk mHSPC.

6. Indicated in patients who meet 'high risk' criteria according to the LATITUDE study. Newly diagnosed metastatic patients who must meet at least two of the following three criteria: visceral metastases and/or Gleason score ≥ 8 and/or bone metastases, regardless of their location, ≥3. A post-hoc analysis of the LATITUDE study, classifying patients into high/low volume, demonstrated benefit of the addition of Abiraterone on progression-free survival in both subgroups, but overall survival only in the high-volume subgroup.

7. The TITAN study included patients with at least one bone and/or visceral metastasis.

8. The benefit of associating primary radiotherapy in low-volume tumors with good functional status (ECOG: 0–1) was tested in the STAMPEDE study, which only recruited ¨de novo¨ metastatic patients.

9. The ARCHES study included patients with at least one bone and/or visceral metastasis.

10. The ARANOTE study included patients with at least one bone and/or visceral metastasis.

physicians frequently need to tailor therapies, as many patients do not fit precisely within the established CHAARTED criteria. This highlights the presence of gray areas that require further clarification to better inform personalized treatment decisions. Key aspects that should be included now and in the future for more informed treatment decisions include:

2.2.1. Clinical prognostic factors

2.2.1.1. Age and life expectancy. Age and life expectancy are crucial in selecting treatment for mHSPC due to the unique challenges older adults face. Geriatric assessments standardize the evaluation process, improving decision-making and enabling maximally tolerated cancer therapies. For patients over 65, estimating non-cancer-related life expectancy and performing geriatric and cognitive screenings are essential, especially before cytotoxic chemotherapy. Addressing reversible frailty aspects before treatment, ensuring universal bone health screening, and selectively using bone antiresorptive therapies are critical for those on long-term ADT. Additionally, decision-making should incorporate patients' goals, quality of life, financial toxicity, social circumstances, and potential barriers to care, reflecting the complexities of treating elderly patients [12].

2.2.1.2. Comorbidities. In treating mHSPC patients, balancing overtreatment and undertreatment is essential, especially given the risks from comorbidities and frailty. Clinicians should conduct comprehensive evaluations of the patient's clinical and functional status, integrating cancer therapy with their overall health and personal goals [12].

2.2.1.3. Intensity of symptoms. The intensity of symptoms and bone marrow reserve are critical factors in mHSPC. Patients with a higher tumor burden (bone, liver, lung or other locations) often experience more severe symptoms, likely associated with a more aggressive form of the disease. In addition, the bone marrow reserve, often compromised by treatments such as chemotherapy and radiation therapy, can also be affected by tumor infiltration in more aggressive disease cases. In such situations, treatment intensification with adjusted doses should be considered, along with close monitoring of hematologic levels, gradually increasing the dosage based on the patient's response [13,14]. However, if the patient is frail and unable to tolerate chemotherapy, a doublet therapy may be preferable, with the option of adding docetaxel if the ECOG performance status and functional reserve improve or continuing the current strategy if no improvement occurs.

2.2.1.4. Metastases.

2.2.1.4.1. Bone metastases. Bone metastasis plays a critical role in the prognosis of metastatic prostate cancer, as it is associated with significant morbidity (pain, pathological fractures, disability) and can influence survival outcomes. Bone metastasis significantly influences prognosis in metastatic PC due to its association with morbidity (pain, fractures, disability) and survival outcomes. The extent of disease seen on bone scans is critical; Noguchi et al. found the percentage of positive area of bone scan (% PABS) to be a reliable predictor of mortality in advanced PC [15]. Additionally, Yücel et al. identified osteolytic bone metastases, especially with tumor masses, as markers of poor survival, emphasizing the impact of metastasis type on prognosis [16]. Baldessari et al. further confirmed that osteolytic lesions lead to faster progression and reduced survival compared to osteoblastic lesions, solidifying their role as a negative prognostic factor [17].

2.2.1.4.2. Visceral metastases. The site and extent of metastases in prostate cancer significantly influence patient survival and outcomes. Gandaglia et al. investigated the impact of metastatic phenotype on survival rates in patients with stage IV PC using data from the Surveillance Epidemiology and End Results – Medicare database. Their analysis included 3,857 patients with various metastatic sites: lymph node alone, bone, visceral, or bone plus visceral metastases. Visceral metastases were associated with the poorest prognosis and highest mortality risk, while lymph node-only metastases had the most favorable outcomes. Bone metastases showed intermediate survival, and patients with both bone and visceral metastases had the worst survival rates, highlighting the aggressive nature of visceral involvement. It was concluded that the metastatic phenotype significantly influences survival outcomes in stage IV prostate cancer [18,19].

2.2.1.4.3. Bulky tumoral masses. Bulky lymphadenopathy or a primary tumor with a Gleason score of 8 or higher – defined as a mass larger than 5 cm – are associated with more aggressive variants of PC and a poorer prognosis [20–22]. Indeed, it has been shown that patients with bulky disease present a poorer OS and PFS [20].

2.2.2. Analytical prognostic factors

2.2.2.1. LDH, CEA, AP and NSE. High serum levels of lactate dehydrogenase are linked to an increased risk of mortality and disease progression in both low-volume and high-volume metastatic PC [23]. Although the prognostic role of carcinoembryonic antigen in PC remains debated [20,21,24,25], elevated alkaline phosphatase levels have been consistently associated with higher risks of mortality and disease progression in mHSPC. Alkaline phosphatase levels are also recognized as independent predictors of overall survival in both high-volume and low-volume cases of HSPC [26]. Additionally, pretreatment serum levels of neuron-specific enolase (NSE) have been shown to correlate with metastatic disease, and patients with elevated NSE levels who received endocrine therapy had significantly poorer cause-specific survival [27]. This suggests that NSE could serve as a useful prognostic factor, particularly in predicting survival outcomes for patients with mHSPC undergoing hormone therapy [27]. Similarly, low levels of hemoglobin at 2–4 months are promising early "on therapy" prognostic biomarkers for survival in patients with newly diagnosed mHSPC who are treated with only ADT [28].

2.2.2.2. PSA kinetics. In PC the time between initial treatment and recurrence is a crucial factor affecting prognosis. Shorter intervals between recurrences often indicate a more aggressive disease and poorer outcomes, with early progression being a sign of increased aggressiveness.

Keizman et al. studied PSA doubling time (PSADT) in patients on intermittent androgen deprivation therapy for biochemically relapsed PC, finding that a shorter PSADT during the first off-treatment interval (median 2.3 months vs baseline 7.34 months) correlated with disease progression [29]. A PSADT under 3 months was linked to worse outcomes. Ceci et al. similarly found that a PSADT of 6 months or less led to significantly shorter event-free survival in patients with biochemically recurrent PC, with a short PSADT associated with higher event rates and poorer prognosis [30].

2.2.3. Pathological prognostic factors

2.2.3.1. High Gleason score and low PSA. The prognostic implications of tumors with high Gleason scores and low PSA levels are of significant interest in PC as these factors are associated with a particularly aggressive disease course and poor clinical outcomes. Mahal et al. conducted a comprehensive analysis of patients with high-grade (Gleason 8–10) PC and low PSA levels. Their study, which involved large datasets from national cancer databases and genomic analysis, revealed that for Gleason 8–10 prostate cancers, a PSA level of ≤2.5 ng/ml was significantly linked to higher prostate cancer-specific mortality (PCSM). The adjusted hazard ratio for PCSM in these patients was 2.70, indicating a markedly increased risk of death. Moreover, these low-PSA, high-grade tumors exhibited higher expression of neuroendocrine markers, suggesting unique biological behavior and potential resistance to standard ADT [31]. Similarly, Wang et al. examined the clinical features and outcomes of metastatic PC with low PSA levels. Their study, encompassing thousands of patients, found that those with Gleason 8–10 tumors and PSA ≤4 ng/ml had higher rates of advanced T4 stage disease and visceral metastasis, and the shortest median OS at 34 months. The findings indicated that a low PSA level was a significant predictor of overall survival for Gleason 8–10 disease, with an adjusted sub distribution hazard ratio (sHR) of 1.52 for PCSM. This further underscores the poor prognosis associated with this subset of PC [32]. Based on these results, it was concluded that tumors with a high Gleason score and low PSA levels tend to progress more rapidly and have a higher risk of death.

2.2.3.2. Histology. The presence of intraductal or cribriform growth patterns in PC is known to exhibit a more aggressive clinical course compared to other forms of prostate cancer. Several studies have highlighted that these cancers tend to progress more rapidly and are associated with a lower survival rate [20,21,33–35].

2.2.3.3. Molecular prognostic factors. Molecular biomarkers such as AR-V7 expression and genomic profiling are being considered as valuable prognostic indicators in mHSPC [36]. Genome sequencing data from the STAMPEDE trial have shown that an increased copy number correlates with a higher risk of disease progression and death in both, high- and low-volume mHSPC [37]. In addition, there is increasing recognition of the molecular landscape of mHSPC, with certain genetic alterations such as mutations in TP53, WNT, and cell cycle genes showing a correlation with disease aggressiveness and prognosis. Emerging evidence indicates that metastasis should be considered as a continuum-spectrum of disease burden rather than a binary state, with local therapies like radiation potentially improving outcomes in oligometastasis. Thus, the study conducted by Deek et al. aimed to investigate the somatic mutational landscape across different stages of metastatic HSPC to provide a biological definition of oligometastatic disease. Researchers conducted a retrospective analysis of men with mHSPC who underwent clinical-grade tumor sequencing (269 primary tumors, 25 metastatic sites), classifying patients into biochemically recurrent, metachronous oligometastatic (≤5 lesions), metachronous polymetastatic (>5 lesions), or de novo metastatic disease. The study found that mutations in driver genes, such as TP53, WNT, and those involved in cell cycle regulation, increased across the mHSCP spectrum. Specifically, TP53 mutations were associated with shorter rPFS and time to CRPC in oligometastatic cases and distinguished patients with polymetastasis with better rPFS. Furthermore, TP53 and DNA double-strand break repair mutations correlated with a higher number of metastases and independently predicted shorter rPFS and earlier development of CRPC. Despite limitations related to the study's retrospective nature, sample size, and the use of a predefined gene set, these findings suggest that somatic mutation profiles can provide a biological perspective on oligometastasis, potentially enhancing existing numerical definitions and informing clinical decision-making [38]. In addition, compound genomic changes affecting the TP53, PTEN, and RB1 tumor suppressor genes are also predictive of the overall survival outcomes in mHSPC [39]. AR abnormalities identified in baseline circulating tumor DNA (ctDNA) are associated with reduced overall survival [40]. In contrast, *SPOP* mutations are linked to extended time to progression and death in patients treated with ARPIs, but not with docetaxel, in mHSPC [41,42].

The meta-analysis by Nguyen et al. examines the utility of a biopsy-based genomic classifier in high-risk prostate cancer, validated in the context of three randomized phase 3 clinical trials (NRG/RTOG 9202, 9413, and 9902). The results show that the genomic classifier (GC) is an independent prognostic factor for distant metastasis (DM), prostate cancer-specific mortality (PCSM), and overall survival (OS). The study highlights the GC's ability to improve risk stratification and personalize decision-making in the treatment of high-risk localized prostate cancer. Additionally, the study suggests that the GC can help identify patients who might benefit from more intensive or less intensive treatments, depending on their individual risk [43]. While this genomic marker has proven to be a first-order prognostic factor, it has not yet been established as a reliable predictor of treatment response. If we extrapolate these findings from the localized high-risk setting to the metastatic setting, one could expect the prognostic profile of this marker to be reproduced. However, it would be far more valuable to validate not only its prognostic role in this scenario but also its potential as a predictor of response – whether to a doublet or triplet therapy regimen. Several clinical trials are currently investigating the use of the Decipher genomic classifier to personalize prostate cancer treatment. Ongoing studies such as NCT03047135 (Phase II), explores the use of olaparib, in

patients with high-risk biochemically recurrent prostate cancer, with Decipher identifying gene expression profiles that may predict treatment sensitivity. Additionally, NCT03413995 (Phase II) investigates rucaparib in metastatic hormone-sensitive prostate cancer, utilizing Decipher to determine genomic signatures associated with therapy response and disease progression. These studies highlight the increasing interest in integrating Decipher into treatment decision-making, not only as a prognostic factor but also as a potential predictor of response to specific therapies. Its validation in these settings could transform the selection of therapeutic strategies for prostate cancer. Unfortunately, while this is a highly logical and relevant goal for this genomic classifier, it has not yet been studied. The ability to move beyond its well-established prognostic role and validate Decipher as a predictor of treatment response – whether for doublet or triplet therapy – would represent a major advance in the personalized treatment of prostate cancer.

Integrating these factors into clinical practice allows for tailored treatment strategies, reflecting the evolving landscape of precision oncology and aiming to optimize therapeutic decisions for individual patients with mHSPC [44]. To evaluate the clinical value of transcriptome-wide expression profiles in high-risk localized and metastatic prostate cancer starting ADT in patients enrolled in the STAMPEDE abiraterone phase 3 trial, Parry et al. developed multi-gene signature scores based on expression data and correlated these with comprehensive, long-term follow-up defined by the protocol [45]. The Decipher score was found to be highly prognostic, particularly for localized cancers. In metastatic cases, factors like cell proliferation, PTEN or TP53 loss, and treatment-resistant cells were key prognostic markers. For localized disease, androgen receptor activity was protective, while interferon signaling – linked to tumor lymphocyte infiltration – was harmful. A specific post-operative radiation score was relevant only for localized disease, highlighting the context-dependent nature of tumor biology in PC. Overall, transcriptome-wide testing demonstrated clinical value, revealing poorer outcomes for localized cancers associated with tumor-promoting inflammation. While there are no definitive predictive biomarkers in mHSPC, several scenarios offer intriguing data. The results of the meta-analysis conducted by Riaz et al. showed that docetaxel overall survival benefit was consistent across genomic classifier groups, but the relative benefit of adding docetaxel to ADT varied significantly by genomic classifier group, with higher-risk disease showing greater benefit. The addition of docetaxel to ADT resulted in a 9% absolute benefit in OS for men with tumors in the lowest-risk genomic classifier group compared to a 25% benefit in the highest-risk group at 3 years [46]. Additionally, gene expression profiling in mHSPC reveals distinct prognostic patterns and varying responses to chemo hormonal therapy. Thus, subgroups identified by high Decipher, luminal B, and AR-low profiles indicate shorter survival when treated solely with ADT. Utilizing expression profiling before treatment provides a foundation for personalized therapy selection, highlighting the potential for biomarker-guided approaches to improve outcomes in mHSPC [47,48].

Insights from mCRPC underscore the significance of *BRCA2* mutations as a prognostic factor. A study by Castro et al. demonstrated that germline DNA damage repair (gDDR) mutations, particularly *BRCA2*, negatively impact patient outcomes, being an independent predictor of poorer survival. The study also found that *BRCA2* carriers respond more favorably to androgen signaling inhibitors compared to taxane therapies, suggesting that assessing *BRCA2* status could inform treatment decisions in mCRPC [49]. Similarly, the CAPTURE study evaluated the prevalence and outcomes of somatic and germline homologous recombination repair (HRR) alterations in 729 mCRPC patients receiving first-line treatment with androgen receptor signaling inhibitors or taxanes. This analysis revealed that patients with *BRCA* mutations had significantly worse rPFS, time to second disease progression and OS compared to both non-*BRCA* mutation patients and those with other HRR mutations [50]. These findings indicate that patients with *BRCA* mutations – regardless of their origin – have poorer outcomes than those with other HRR mutations, and both groups perform worse than patients without HRR mutations.

2.2.4. Imaging prognostic factors

In recent years, the adoption of PSMA PET/CT has significantly increased for both initial staging and assessing biochemical recurrence in PC patients. This shift is driven by the superior performance of PSMA PET/CT compared to traditional imaging methods [51]. PSMA PET/CT provides superior detection capabilities for both primary and metastatic lesions, enabling precise localization of disease and redefining oligometastatic disease states. Its ability to identify lesions with high specificity has allowed for tailored therapeutic interventions, such as stereotactic body radiotherapy (SBRT) for isolated metastases and better stratification of patients eligible for radioligand therapies like 177Lu-PSMA-617. Emerging evidence from studies, including the Ferro review, suggests that advanced imaging can facilitate decision-making for radiotherapy to the primary tumor and optimize outcomes in patients with low metastatic burden [19,52–56]. This aligns with data from the STAMPEDE and HORRAD trials, which indicate the potential survival benefit of aggressive local therapy in carefully selected patients [57,58].

PSMA PET/CT can detect metastatic disease in patients previously considered nonmetastatic and reveal a higher disease burden than conventional imaging. This can lead to discrepancies where patients classified as “high-volume” based on PSMA PET/CT may be deemed “low-volume” by CT and bone scans [52]. The enhanced sensitivity of PSMA PET/CT has led to significant changes in management plans, as demonstrated by the CONDOR trial, which involved patients with biochemical recurrence and unclear results from conventional tests. In this study, 64% of patients experienced alterations in their intended disease management. The increased sensitivity of functional tests, such as PSMA PET/CT, enhances the likelihood of detecting metastatic disease or locoregional recurrence. Additionally, these tests may aid in assessing patients’ disease status, potentially moving them from low-volume to high-volume classifications [55]. However, while there is robust evidence supporting the improved sensitivity of these functional tests in identifying metastatic disease and informing therapeutic strategies, no data currently exists to

indicate that PET scans can effectively transition patients from low-volume to high-volume status.

2.2.5. Novel biomarkers

The future of therapy modulation and personalization in mHSPC lies in understanding the disease's biology and biomarkers. Building on the advancements in personalized treatments for mCRPC, the potential to improve the balance between benefit and burden of systemic therapies in mHSPC is promising [46]. The distinction between prognostic and predictive factors can sometimes be ambiguous, even in real clinical practice. While meta-analyses suggest a benefit of triplet therapy over doublet therapy in patients with de novo high-volume mHSPC, there is no direct comparative study that confirms this superiority. In this sense, we have transformed a poor prognostic factor – de novo high-volume mHSPC – into a criterion for selecting patients more suitable for triplet therapy over doublet therapy, effectively making it a predictive factor of good response to triplet therapy according to these meta-analyses. However, this reasoning cannot be extrapolated to other parameters analyzed, and thus, they should continue to be considered prognostic factors rather than predictive ones until new specific evidence emerges. Key examples include PSA kinetics, circulating tumor DNA (ctDNA), AR-V7 expression, PSMA expression, and genomic classifiers like Decipher. PSA kinetics serves as a prognostic marker for disease aggressiveness and response to therapy. Circulating tumor DNA detects actionable mutations like BRCA1/2 alterations, guiding PARP inhibitor use. AR-V7 expression indicates resistance to androgen receptor inhibitors, aiding treatment optimization. PSMA expression predicts responses to PSMA-targeted therapies, including 177Lu-PSMA-617, while genomic classifiers help stratify patients by risk and guide treatment intensification. Additionally, the Tataru study highlights Fascin-1 (FSCN1) as an exploratory biomarker for prostate cancer. While FSCN1 shows potential as a serological marker, its role in mHSPC remains limited due to insufficient evidence linking it to disease severity or treatment outcomes [59]. These findings emphasize the need for further research to validate FSCN1 and other novel biomarkers for personalized care. In addition, patients with high SUV on PSMA PET may benefit from PSMA-targeted therapies, while those with PTEN or PIK3A/AKT mutations might require AKT inhibitors. MSI high or TMB high tumors may respond to PD-1 inhibitors, and HRR mutations can be treated with PARP inhibitors. Optimal PSA response could lead to deintensified treatment, underscoring the importance of molecular profiling to guide treatment decisions [60].

The prevalence of germline and somatic *BRCA1/2* and homologous recombination gene mutations in metastatic prostate cancer, along with the success of PARP inhibitors, has sparked numerous trials combining PARP inhibitors with other therapies in mHSPC (Amplitude, NCT04497844; Talapro-3, NCT04821622; EvoPAR-PR01 NCT06120491). The FDA and EMEA approval of ^{177}Lu-PSMA-617 for mCRPC has also paved the way for trials exploring its use in mHSPC, particularly due to the high expression of PSMA in hormone-sensitive disease. Ongoing trials are investigating the combination of ^{177}Lu-PSMA-617 with chemotherapy (e.g., UpFrontPSMA, NCT04343885) or androgen receptor signaling inhibitors (e.g., PSMAddition, NCT04720157) (Table 1) [61–65]. The rapid evolution of predictive biomarkers is shaping future trials in mHSPC, where treatment strategies will be defined by molecular, PSA, imaging, and other individualized data.

3. Discussion

Six questions were asked to the expert panel and they reached a consensus for the answer, with the goal of providing guidance on personalizing therapy and improving clinical outcomes for this diverse patient population. The methodology used for expert selection and consensus statements involved identifying a panel of specialists with extensive experience in the management of mHSPC. The questions were collaboratively formulated to address key clinical uncertainties deemed relevant for optimizing treatment decisions. The panel members analyzed the available evidence and clinical data, engaging in in-depth discussions for each question. Consensus was achieved through group

Table 1. Selected ongoing phase 2/3 trials in mHSPC patients.

Study	Trial Agent	Control Arm	Estimated, n	Inclusion Criteria	Primary Outcome
UpFrontPSMA (Phase 2)	^{177}Lu-PSMA-617 + docetaxel	Placebo + docetaxel	140	mHSPC, PSMA-positive disease	Proportion of patients with undetectable PSA (≤0.2 ng/L) at 12 months after study treatment commencement
PSMAddition (Phase 3)	^{177}Lu-PSMA-617 + ARPI +ADT	ARSI + ADT	1126	mHSPC, PSMA-positive disease	rPFS
AMPLITUDE (Phase 3)	Niraparib + ARPI + ADT	Placebo + ARPI + ADT	788	mHSPC with germline or somatic HRR gene alteration	rPFS
TALAPRO-3 (Phase 3)	Talazoparib + ARPI + ADT	Placebo + ARPI +ADT	550	mHSPC with DDR mutations	rPFS
EvoPAR-PR01 (Phase 3)	Saruparib (AZD5305) + + physician's choice NHA (Abiraterone, Darolutamide, or Enzalutamide)	Placebo + + physician's choice NHA (Abiraterone, Darolutamide, or Enzalutamide)	1800	HRRm and Non-HRRm mHSPC	rPFS

ADT: androgen deprivation therapy, ARPI: androgen receptor pathway inhibitors, DDR: DNA damage response, HRR: homologous recombination repair, HRRm: Homologous recombination repair mutation, mHSPC: Metastatic hormone sensitive prostate cancer, NHA: novel hormonal agents, PSMA: Prostate-Specific Membrane Antigen, rPFS: radiographic progression-free survival.

deliberation, incorporating perspectives from all experts, with final responses based on the best available evidence and clinical judgment. While this was not a formal Delphi process, the structured discussions aimed to provide practical guidance for therapy personalization in mHSPC.

3.1. Question #1: how should patients be selected for doublet or triplet therapy?

Consensus answer: Due to the lack of validated predictive biomarkers and randomized clinical trials comparing triplet therapy to the combination of ADT and an ARPI, determining which patients may benefit more from each regimen remains a challenge (Figure 2). Multiple factors – including disease characteristics, patient profiles, and treatment considerations – play a role in this decision-making process. Patients with low-volume disease, as defined by CHAARTED criteria, may not derive additional benefit from adding docetaxel + darolutamide/AAP (AAP = abiraterone acetate + prednisone). In contrast, those with synchronous and high-volume disease are more likely to benefit from adding docetaxel to ADT and darolutamide/AAP. The choice of treatment regimen is significantly influenced by the physician's interpretation of available data, clinical judgment regarding the patient's tolerance for chemotherapy, and the physician's comfort level in managing potential adverse effects. Older patients with poor performance status (ECOG ≥2), comorbidities like neuropathy, limited social support, or those who prefer to avoid chemotherapy are more likely to be considered for doublet treatment. While docetaxel is relatively affordable and administered over a short period (six cycles within 4 to 5 months), these factors should be carefully weighed when choosing a treatment approach [66].

3.2. Question #2: Is there a single optimal therapy scheme to maximize disease control while balancing treatment burden?

At present, there is no universally optimal treatment regimen for maximizing disease control while minimizing treatment burden in mHSPC. Therapeutic strategies must be tailored to each individual, taking into account the prognosis of each case, which is determined by personal, clinical, pathological, and molecular factors. While triplet therapy (ADT + darolutamide/AAP + docetaxel) may benefit patients with high-volume or synchronous disease, doublet therapy (ADT + darolutamide/AAP) may be sufficient for those with low-volume or metachronous disease. The choice of therapy should also consider the patient's ability to tolerate treatment-related toxicities and the overall impact on quality of life, highlighting the importance of a multidisciplinary approach in developing individualized treatment plans.

3.3. Question #3: can clinical and biologically based disease subgroups guide personalized and adaptive strategies?

Consensus answer: Various biological, clinical, and molecular markers have been proposed to personalize prognostic assessments for patients, with the potential to guide the selection of the most effective treatment for each individual. However, as the clinical implications of incorporating these markers into

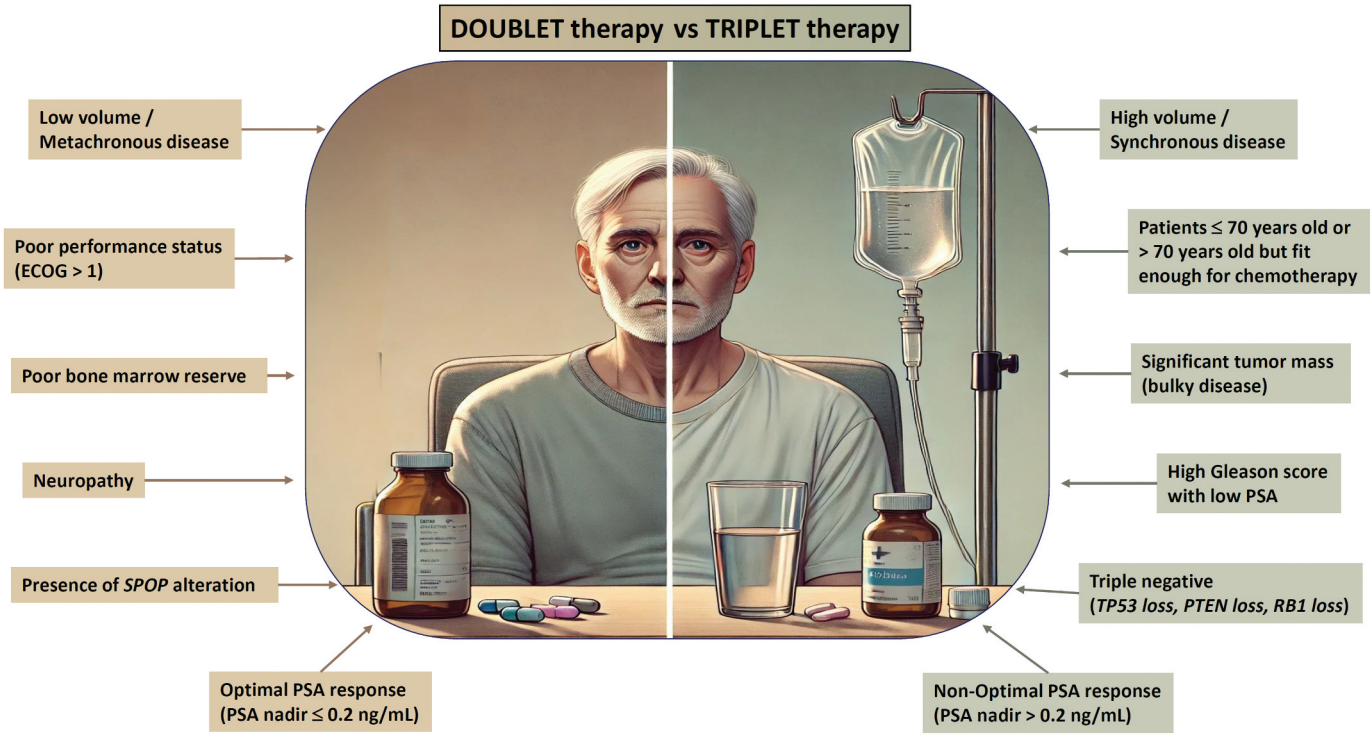

Figure 2. mHSPC: Doublet vs Triplet therapy.

ECOG: Eastern Cooperative Oncology Group, PSA: prostate-specific antigen, PTEN: Phosphatase and tensin homolog, RB1: retinoblastoma protein, SPOP: speckle-type POZ protein, TP53: tumor protein p53.

*Image generated with IA-Gen (DALL-E).

treatment decisions remain uncertain, the authors advocate for further research that includes variables such as histological subtypes, molecular profiles, and radiological data. Such studies are crucial to understanding the impact of personalized treatment approaches on oncological outcomes. Given the challenges of conducting clinical trials to evaluate these implications, real-world evidence and data from large clinical registries represent valuable resources to address these critical questions.

3.4. Question #4: how can we optimize management of the primary tumor and local symptoms within different strategies for mHSPC?

Consensus Answer: Local tumor burden can significantly impact quality of life, and radiation therapy is a viable option for managing symptomatic disease [53]. Studies have demonstrated that radiotherapy achieves high response rates in patients with local symptoms [54], and significantly reduces the occurrence of new symptomatic events compared to patients who do not undergo such treatment [67]. In addition to these benefits, radiotherapy has shown survival advantages in patients with low-volume disease. Findings from arm H of the STAMPEDE trial, as well as recent results from the PEACE-1 trial, indicate that local radiation of the primary tumor not only reduces symptomatic genitourinary events but also improves quality of life across both low-volume and broader patient populations. These studies further underscore the role of radiotherapy in maintaining quality of life and extending symptomatic event-free survival when added to primary tumor management, thereby supporting its use in carefully selected patients [68–70].

3.5. Question #5: how can PET-PSMA be applied in staging hormone-sensitive prostate cancer?

Consensus answer: Currently, evidence is lacking on whether therapeutic decisions informed by PET-PSMA staging improve patient outcomes. Since a positive PET-PSMA finding may classify a patient as metastatic – thereby precluding surgical options – it is essential to involve the patient in the decision-making process. Patients should be informed of the possibility of surgery and the subsequent confirmation of metastatic status based on persistent PSA levels. In this context, the therapeutic approach is somewhat better studied than staging based solely on PET-PSMA. This aligns with current recommendations against performing PET-PSMA if the results do not influence treatment decisions, but with an emphasis on involving the patient in the decision-making process.

3.6. Question #6: what type of clinical trial would clarify the benefits of adding docetaxel to an ARPI backbone?

Consensus answer: A randomized controlled trial in which ADT + darolutamide/AAP is administered to all patients as standard care, with docetaxel added only in the study arm, would provide the optimal framework for clarification. To gain further insights into benefits across different subgroups, a predefined subgroup analysis should be included. However, limitations may still arise based on the specific definitions of disease volume used in the trial.

4. Future perspective

In the coming years, advancements in clinical trials and emerging technologies will likely shape new treatment strategies for different subgroups of mHSPC patients. Ongoing and recently completed clinical trials may provide valuable insights into better patient stratification and personalized treatment options. For instance, studies are examining the role of HRR alterations and the impact of combining treatments with PARP inhibitors, the potential of PSMA- radioligand therapy, and the role of PTEN loss expression in mHSPC and its implications for treatment combinations with AKT inhibitors. Additionally, the long-term toxicity of intensified frontline approaches incorporating PARP inhibitors or RLT, especially regarding hematologic toxicity reduction, will need careful evaluation.

De-escalation strategies may also play an important role in mHSPC management, as exemplified by the pragmatic EORTC GUCG 2238 De-escalate trial (NCT05974774), which will assess intermittent AR blockade, with the option to add docetaxel and radiotherapy based on investigator discretion. Early response assessments, while not yet validated for clinical practice, could help tailor treatment intensity and optimize outcomes [71].

Incorporating transcriptional signatures, such as those identified by Decipher, and leveraging artificial intelligence to guide treatment decisions are promising areas of development. Integrating "omics" data – including radiomics, genomics, proteomics, metabolomics, and epigenomics – into the initial assessment and ongoing management of mHSPC patients may enable a more tailored approach to treatment. Personalized therapy could be further refined by identifying and targeting new molecular alterations that enhance treatment outcomes, with molecular profiles initially determined through next-generation sequencing (NGS) to detect a wide array of actionable targets. A networked oncology approach, such as using a molecular tumor board, would facilitate comprehensive evaluations and personalized treatment planning, as has been done in other cancers.

In the absence of large randomized controlled trials, real-world data registries and pooled big data analyses will become essential tools for identifying optimal treatment strategies. Molecular imaging and biomarkers will also likely gain importance in guiding these individualized approaches. Other potential analyses to support personalized treatment may include developing multivariate equations to predict individualized probabilities of progression and mortality over specific time intervals, utilizing variables and outcomes from pivotal studies. This would enable indirect comparisons of individualized outcomes across various treatment regimens. Alternatively, consolidating records from pivotal studies to allow direct comparisons while acknowledging potential biases. These biases, likely smaller than those in clinical practice studies, could be identified and adjusted.

The evolving landscape of diagnostic and therapeutic strategies in prostate cancer underscores the need for continual

innovation and integration of advanced technologies. Current trends emphasize refining imaging modalities, improving biomarker identification, and optimizing personalized treatment approaches.

One of the most promising advancements is the integration of artificial intelligence (AI) and machine learning (ML) into clinical decision-making. These technologies have shown potential to enhance diagnostic accuracy, streamline workflow efficiency, and improve outcome predictions. For example, AI algorithms applied to PSMA PET/CT imaging data can automatically identify metastatic lesions with high precision, reducing interobserver variability [72]. Similarly, ML models are being developed to predict treatment response based on genomic and imaging data, aiding clinicians in tailoring therapy to individual patient profiles [73,74].

Recent studies have also highlighted the utility of AI in risk stratification, where deep learning algorithms analyze complex datasets – including histopathology, radiology, and clinical records – to identify patterns associated with disease progression and treatment outcomes [74,75]. Additionally, integrating AI-driven decision support systems into clinical workflows can provide real-time recommendations, ensuring evidence-based and timely treatment interventions [72,75]. Despite the potential, significant challenges remain, including the need for robust validation, regulatory approval, and addressing the ethical implications of AI-driven decision-making in healthcare [76]. Future research should focus on multicenter collaborations to standardize AI and ML applications, ensuring their reproducibility and clinical utility [73,75]. The application of these technologies represents a paradigm shift in the management of prostate cancer, enabling a more precise, efficient, and personalized approach to care.

Acknowledgments

The authors acknowledge the use of ChatGPT, a generative AI tool developed by OpenAI (version January 2025), in proofing. ChatGPT was utilized to refine the manuscript's language, ensuring it met professional standards for readability and coherence. All scientific content, analysis, and conclusions were independently developed and verified by the authors.

Additionally, the authors disclose the use of IA-Gen (DALL-E) software in the creation of Figure 2, which was utilized to generate illustrative content for visual representation purposes.

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Disclosure statement

Ángel Borque-Fernando has received honoraria for participation in training events from Asofarma, Astellas, Astra-Zeneca, Bayer, GP Pharm, HealthMDx, Ipsen, Janssen, Lacer, MSD; honoraria for participating in Advisory Board from Astellas, Astra-Zeneca, Bayer, Janssen, MSD; support for attending meetings from Astellas, Astra-Zeneca, Bayer, Ipsen, Janssen, Recordati.

Teresa Alonso-Gordoa reports Advisory role or speaker's fee from Lilly, Bayer, Johnson & Johnson, Astellas, Eisai, Roche, Ipsen, MSD and Adacap. Research Grant from Johnson & Johnson and IPSEN.

María José Juan-Fita has received honoraria for consulting, participation in training events or advisory boards from Bayer, Astellas Pharma, Johnson and Johnson, Merck, IPSEN, MSD, Astra Zeneca; support for attending meetings from IPSEN, Bayer and Johnson and Johnson.

Fernando Lopez Campos has received honoraria for participation in training events from Astellas, Astra-Zeneca, Bayer, Janssen; honoraria for participating in Advisory Board from Astellas, Astra-Zeneca, Bayer, Janssen, MSD, Recordati; support for attending meetings from Astellas, Astra-Zeneca, Bayer, Ipsen, Janssen, Recordati.

Daniel Adolfo Pérez-Fentes has received honoraria for consulting, participation in training events or advisory boards from Bayer, Astellas Pharma, Janssen support for attending meetings from Bayer, Astellas Pharma, Janssen.

Antoni Vilaseca has received honoraria for consulting and participation in training events from Bayer, Johnson&Johnson, Astellas, Recordati, Ipsen and Accord Healthcare.

Cristina Moretones Agut is an employee of Bayer Hispania S.L.

Paola Usán is an employee of Bayer Hispania S.L.

Pablo Maroto Rey reports Advisory board role for Pfizer, Bayer, Ipsen, Novartis, Janssen, Astellas and he has received Travel grants from Bayer, Ipsen, Pfizer, Merck.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing and editorial support were provided by Content Ed Net with funding from Bayer Hispania.

Funding

This article is based on a meeting organized and funded by Bayer Hispania.

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