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Treatment Landscape of Prostate Cancer in the Era of PSMA Radiopharmaceutical Therapy

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The treatment landscape of prostate cancer is quite complex because of the many therapeutic options available in different disease settings (hormonal treatments, chemotherapy, poly(adenosine diphosphate ribose) polymerase inhibitors, radiopharmaceutical therapy). Since in most cases we do not have comparative studies between these different agents, the best therapeutic sequence in patients with prostate cancer remains unsolved. In this review, we describe the different systemic therapeutic options available in each disease setting from localized disease to metastatic castration-resistant disease. We also indicate when to use each of these therapeutic options in the therapeutic sequence on the basis of the results of the available studies. A special focus of this review is the place of prostate-specific membrane antigen radiopharmaceutical therapy in the treatment algorithms.

Key Words: radiopharmaceuticals; advanced prostate cancer; radiopharmaceutical therapy; systemic therapies; mCRPC; mHSPC

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In the past 20 y, the landscape of advanced prostate cancer (PC) has changed dramatically. Since the publication of the TAX-324 and SWOG-9916 trials, which established docetaxel as the first survival-prolonging systemic therapy for patients with metastatic castration-resistant PC (mCRPC), a wide range of different treatment modalities has been shown to prolong overall survival (OS) in this setting (Fig. 1) (*1–3*). Some of these therapeutic strategies have improved OS even in earlier settings such as nonmetastatic CRPC (nmCRPC) (*4–6*), metastatic hormone-sensitive PC (mHSPC) (*7–16*), high-risk localized disease (*17*), and high-risk biochemical recurrence (*18*).

Since all these therapeutic options are now available for the treatment of patients with PC in different disease settings, and since in most situations there is a lack of direct comparison studies between these different therapies, the therapeutic choice for each individual patient in each specific disease setting is becoming increasingly complex. The aim of this review is to summarize the currently available evidence. Since high-level evidence to help treatment decisions is often missing, when appropriate we use in this review the voting results from the Advanced PC Consensus Conference (APCCC) of 2024 (*19*). A special focus of this review is the place of prostate-specific membrane antigen (PSMA) radiopharmaceutical therapy in the treatment algorithms.

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HIGH-RISK LOCALIZED DISEASE

In 2021, the results of STAMPEDE arms G and J regarding patients with nonmetastatic disease were published (*17*). In that study, the addition of androgen deprivation therapy (ADT) for 3 y plus abiraterone with or without enzalutamide for 2 y to radiation therapy (RT) to the prostate was evaluated in patients with clinically node-positive (cN1) disease and patients with high-risk node-negative (cN0) disease (defined as having ≥2 of the following: >cT3, Gleason score >8, prostate-specific antigen [PSA] ≥40 ng/mL) compared with radiotherapy plus ADT for 3 y. The trial also enrolled patients with relapsing nonmetastatic disease with high-risk features (≤12 mo of total ADT with an interval of ≥12 mo without treatment and PSA concentration ≥4 ng/mL with a doubling time of <6 mo, or a PSA concentration ≥20 ng/mL, or nodal relapse). However, patients with relapsing disease were only 3% of the total population.

The experimental arm was shown to improve metastasis-free survival and OS (hazard ratio, 0.54 [95% CI, 0.43–0.68] and 0.6 [95% CI, 0.48–0.73], respectively). There was no difference in metastasis-free survival or OS when enzalutamide and abiraterone were administered concurrently compared with administration of abiraterone alone; thus, adverse events were more frequent (58% vs. 38%). According to the results of the study, the guidelines of the National Comprehensive Cancer Network and European Association of Urology recommend using 2 y of abiraterone when offering RT to the prostate in combination with long-term ADT for patients with cN1 or with cN0 high-risk disease according to the STAMPEDE definition (*20*,*21*). The trial used conventional imaging (CT and bone scintigraphy), and it is clear that with more sensitive imaging, in particular PSMA PET/CT, some of the patients would have had at least low-volume mHSPC.

To date, only small phase I/II trials have evaluated PSMA radiopharmaceutical therapy in patients with localized disease (*22*,*23*). Golan et al. conducted a clinical trial with 14 patients with high-risk localized PC (*22*). Before radical prostatectomy (RP), patients were treated with 2–3 doses of ^{177}Lu-PSMA-I&T (7.4 GBq with a 2-wk interval between cycles). The median PSA reduction registered was 3.45 and 4.3 ng/mL after 2 and 3 ^{177}Lu-PSMA doses, respectively. In the LuTectomy trial, 20 patients

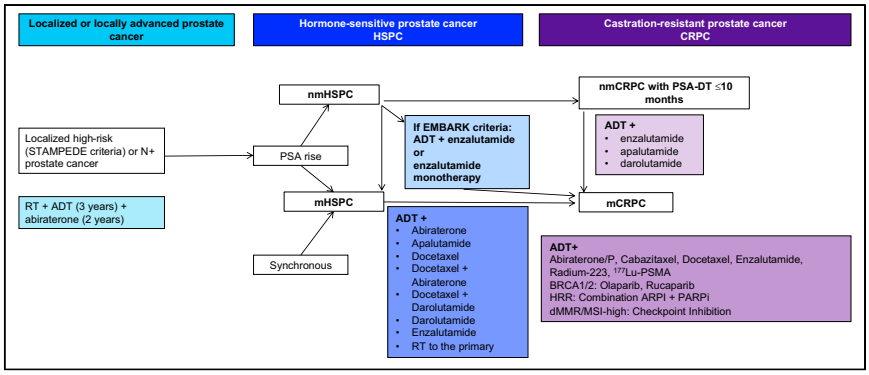

FIGURE 1. Treatment landscape of advanced PC. dMMR = deficient mismatch repair; DT = doubling time; MSI = microsatellite instability; nmHSPC = nonmetastatic HSPC.

received 1–2 doses of ^{177}Lu-PSMA-617 (5 GBq with a 6-wk interval between cycles) before RP (*23*). The primary endpoint was tumor-absorbed radiation dose, defined as the maximum dose in grays within the prostate and the involved lymph nodes. Almost half the patients achieved a 50% PSA reduction at 6 wk after receiving ^{177}Lu-PSMA, and the treatment was well tolerated. At restaging PSMA PET/CT after the treatment and before surgery, a partial PSMA response was achieved in 11 (55%) of 20 patients. Progressive PSMA disease with an increased SUV_{max} occurred in 1 (5%) of 20 patients. The remaining 8 (40%) patients had stable PSMA disease. All patients underwent RP, and no surgical complications were attributed to ^{177}Lu-PSMA.

In these 2 trials were used 2 different molecules (^{177}Lu-PSMA I&T vs. ^{177}Lu-PSMA 617), different numbers of cycles (2–3 vs. 1–2 cycles), different dosages (7.4 vs. 5 GBq), and different intervals between cycles (every 2 wk vs. every 6 wk). Interestingly, in both studies, ^{177}Lu-PSMA was administered without ADT (*22*,*23*). ^{177}Lu-PSMA seemed to show some efficacy as a neoadjuvant treatment before RP in patients with high-risk localized disease. However, these preliminary results need to be verified in bigger, randomized trials.

HIGH-RISK BIOCHEMICAL RECURRENCE

Results from the randomized phase 3 EMBARK trial were published in 2023 (*18*). This trial included patients with nonmetastatic high-risk biochemical recurrence, defined as a PSA doubling time of 9 mo or less and a PSA level at least 2 ng/mL above the nadir after RT or at least 1 ng/mL above the nadir after surgery, with or without postoperative RT. Conventional imaging was used for staging. Of the participants, 25% had previously undergone RP alone, 26% received RT alone, and 49% had both RP and postoperative RT. Patients were randomized to receive 37 wk of ADT alone, enzalutamide alone, or a combination of enzalutamide and ADT. Treatment was suspended at week 37 if the PSA level was less than 0.2 ng/mL and was restarted when the PSA level was at least 5 ng/mL (if the patient had not had previous RP) or at least 2 ng/mL (if the patient had previously had RP). Patients who did not reach a PSA of 0.2 ng/mL or less at week 37 continued to receive their assigned treatments until progression or until an unacceptable adverse event occurred. Regarding metastasis-free survival, both the combination therapy and enzalutamide alone showed superior outcomes to ADT alone. EMBARK used conventional imaging, and it is clear that with more sensitive imaging, in particular PSMA PET, many of these patients have at least low-volume mHSPC. A poster presentation at the American Society of Clinical Oncology 2023 meeting on 183 EMARK-like patients staged by PSMA PET reported local relapse in 9%, pelvic nodal disease in 40%, distant lymph node metastases in 39%, and bone metastases in 23% (*24*). The use of androgen-receptor pathway inhibitor (ARPI) alone or in combination with ADT may change the natural history of the disease and has implications on the available treatment options at progression.

To our knowledge, there are no published data about the use of ^{177}Lu-PSMA in the biochemical recurrence setting. However, there is an ongoing phase I/II trial that is evaluating ^{177}Lu-PSMA I&T in combination with high-dose-rate brachytherapy in patients with locally recurrent PC after previous definitive RT (*25*).

NOTEWORTHY

- The treatment landscape in PC is becoming increasingly complex, as we have different therapeutic options available in different disease settings without, in most cases, having comparative studies between the different available drugs.
- No single therapeutic sequence is valid for all patients. In each therapeutic choice, several factors must be considered: previous treatments; performance status; comorbidity; presence or absence of symptoms; clinical, biologic, and genomic characteristics of the disease; patient's preferences; availability of drugs.
- To date, the strongest evidence on the efficacy of PSMA radiopharmaceutical therapy is in the metastatic castration-resistant setting; this treatment should therefore be used only in this setting outside of clinical trials
- Because several ongoing studies are evaluating the efficacy of PSMA radiopharmaceutical therapy in earlier settings, its use in the therapeutic algorithm is anticipated.

MHSPC SETTING

For about a decade, ADT monotherapy has no longer been the standard of care in patients with mHSPC (*20*,*21*,*26*). Several studies have demonstrated that combination therapies are able to improve OS compared with ADT monotherapy (Figs. 2 and 3) (*26*). ADT plus docetaxel was the first combination shown to improve outcomes for patients with mHSPC, especially in patients with high-volume disease (*7*–*9*). Subsequently, the addition of an ARPI (abiraterone, darolutamide, enzalutamide, or apalutamide) to ADT has also been shown to improve OS compared with ADT alone (*10*–*14*). Recently, data from the ARANOTE study were presented (*27*). In this trial, the combination of ADT plus darolutamide improved radiographic progression-free survival (rPFS) compared with ADT alone. At a median follow-up of approximately 25 mo, OS data of this study were not yet mature. Finally, 2 phase 3 clinical trials, PEACE 1 and ARASENS, showed that triplet systemic therapy consisting of ADT plus 6 cycles of docetaxel plus abiraterone or darolutamide improves OS in comparison to doublet therapy consisting of ADT plus 6 cycles of docetaxel (*15*,*16*). We are not aware of any randomized evidence, to date, on whether systemic triplet therapy improves outcomes in comparison to doublet therapy with ADT plus an ARPI (*28*). At the APCCC 2024

	Synchronous	Metachronous	Trials
ADT	**Yes**	**Yes**	
+ Abiraterone/Prednisone[2] + Enzalutamide + Apalutamide + Darolutamide[3]	**Yes,** one of the options	**Yes,** one of the options	LATITUDE (synchronous) STAMPEDE TITAN ARCHES ENZAMET ARANOTE
+ Docetaxel + Abiraterone/Prednisone[3] + Docetaxel + Darolutamide	**Yes,** consider if fit for chemotherapy	**Only selected patients,** fit for chemotherapy	PEACE-1 (synchronous) ARASENS
+ Radiation primary tumor[4]	Only selected cases	Only selected cases in case of local recurrence and complications	HORRAD STAMPEDE PEACE-1

1. Based on CHAARTED or LATITUDE respectively, careful interpretation if PSMA PET is used for staging
2. Approval: only LATITUDE high-risk, with at least 2 of the 3 following risk factors defined: (1) Gleason score ≥8; (2) at least 3 bone metastases; (3) visceral metastases (without considering lymph node involvement).
3. No approval.
4. Not in all studies overall survival benefit, but in PEACE-1 there was a reduction in the risk of severe local complications (catheterization, double J stent, nephrostomy, salvage radiation therapy or salvage radical prostatectomy, or transurethral resection of the prostate).

FIGURE 2. Treatment options in mHSPC for high volume/risk.

meeting, panelists voted on questions regarding the use of systemic triplet therapy in different scenarios based on timing of metastatic presentation (de novo vs. metachronous) and volume of disease according to the CHAARTED criteria (low vs. high volume) (*19*). In none of the 4 subgroups analyzed (synchronous low volume, synchronous high volume, metachronous low volume, and metachronous high volume) was a consensus reached. However, in patients with high-volume disease, 94% and 84% of the panelists voted in favor of recommending triplet therapy at least for selected patients.

According to the evidence described, the current international guidelines recommended ADT plus ARPI with or without docetaxel as the standard-of-care systemic treatment in patients with mHSPC (*20*,*21*).

Studies on patients with mHSPC have evaluated the effect of RT to the primary (*29*–*32*). RT to the primary did not improve OS in the overall population in any of the randomized trials. For patients with low-volume synchronous mHSPC, RT to the primary in addition to ADT improved OS in a prespecified and prepowered subgroup analysis for 1 study (STAMPEDE) but not in the 2 other phase 3 trials (HORRAD and PEACE-1) (*29*,*30*,*32*). The only evidence regarding the effect of adding both RT to the primary tumor and an ARPI to the standard of care for patients with PC comes from PEACE-1 (*32*). For patients with low-volume disease, the standard of care (ADT ± docetaxel) plus abiraterone plus RT to the primary tumor improved rPFS, but not OS, in comparison to the standard of care plus abiraterone. In the PEACE-1 trial, RT to the primary reduced the occurrence of serious genitourinary events in patients independently of volume of disease. Interestingly, at the APCCC meeting there was a consensus to recommend ADT plus ARPI plus RT to the primary tumor in most patients with synchronous low-burden mHSPC (*19*).

Since all the studies that evaluated combination systemic therapies and RT to the primary used conventional imaging, it is unclear whether we can extrapolate the results to patients with metastatic disease diagnosed only with next-generation imaging such as PSMA PET/CT. Therefore, in daily practice, clinicians face the increasingly challenging question of which treatment to recommend for patients with synchronous oligometastatic PC.

There is no randomized trial evidence for synchronous oligometastatic HSPC suggesting a benefit of systemic therapy plus treatment of the primary plus metastasis-directed therapy for all metastases, nor is there a formal and generally accepted definition for oligometastatic disease. At the APCCC meeting, there was no consensus to recommend metastasis-directed therapy in most patients with synchronous low-burden mHSPC on conventional imaging or on next-generation imaging (*19*). However, there was a consensus to recommend metastasis-directed therapy for selected patients with synchronous low-burden mHSPC on next-generation imaging.

PSMA radiopharmaceutical therapy is currently not a standard of care in the mHSPC setting. Privé et al. conducted a prospective pilot study assessing the efficacy of ^{177}Lu-PSMA-617 in 10 patients with mHSPC with a maximum of 10 metastatic lesions on PSMA PET/CT (*33*). These patients received 2 cycles of ^{177}Lu-PSMA-617 (3 GBq the first cycle followed by a second cycle with 3–6 GBq after 7–9 wk) without ADT. Half the patients experienced a PSA reduction of more than 50%, with 1 patient achieving an undetectable PSA level. At 24 wk after the second cycle, 5 patients displayed at least a partial response, with 1 patient revealing a complete response, and the disease progressed in 4 patients. There are several ongoing studies evaluating ^{177}Lu-PSMA in mHSPC both as monotherapy and in combination with the standard of care. The results of the UpFrontPSMA trial were recently published (*34*). This is a randomized, phase 2 trial in which patients with high-volume mHSPC were randomized to receive ADT plus 2 cycles of ^{177}Lu-PSMA-617 7.5 GBq every 6 wk followed 6 wk later by 6 cycles of docetaxel or ADT plus 6 cycles of docetaxel. The primary endpoint was undetectable

	Synchronous	Metachronous	Trials
ADT	**Yes**	**Yes, alternatively Metastases-directed therapy ± ADT or Watchful Waiting**	Metachronous: STOMP, ORIOLE, SABR-COMET, POPSTAR
+ (Abiraterone/Prednisone[2]) + Enzalutamide + Apalutamide + Darolutamide	**Yes,** one of the options	**Yes,** one of the options if ADT is used	STAMPEDE TITAN ARCHES ENZAMET ARANOTE
+ Docetaxel + Abiraterone/Prednisone[3] + Docetaxel + Darolutamide	Only selected cases	No	PEACE-1 (synchronous) ARASENS
+ Radiation primary tumor	**Yes**	Only selected cases in case of local recurrence and complications	HORRAD STAMPEDE PEACE-1
Metastases directed therapy	Only selected cases	See above	**Synchronous**: EXTEND, PMID: 31971828, 32524295 **Metachronous**: STOMP, ORIOLE, SABR-COMET, POPSTAR

1. Based on CHAARTED or LATITUDE respectively, careful interpretation if PSMA PET is used for staging
2. Approval: only LATITUDE high-risk, with at least 2 of the 3 following risk factors defined: (1) Gleason score ≥8; (2) at least 3 bone metastases; (3) visceral metastases (without considering lymph node involvement).
3. No approval.

FIGURE 3. Treatment options in mHSPC for low volume/risk.

PSA (≤0.2 ng/mL) at 48 wk. Twenty-five (41%) of 61 patients in the experimental arm had undetectable PSA at 48 wk, compared with 10 (16%) of 61 patients in the ADT-plus-docetaxel group (odds ratio, 3.88; 95% CI, 1.61–9.38; $P = 0.0020$). Treatment with ^{177}Lu-PSMA was generally well tolerated. Despite the fact that ADT plus docetaxel is currently no longer the standard of care, these data may suggest that ^{177}Lu-PSMA could potentially have a role in the management of mHSPC. The randomized phase 3 PSMAddition study randomizing patients with mHSPC to ADT plus ARPI plus 6 cycles of ^{177}Lu-PSMA-617 has completed enrollment (*35*). The results of this study will clarify the role of ^{177}Lu-PSMA in this setting.

GENERAL CRPC

Castration-resistant PC refers to the condition in which PC continues to progress despite ADT.

A molecular pathologic examination of tumor tissue to identify therapy-relevant alterations (especially BRCA1/2 and other homologous recombination defects [HRR alterations], defective mismatch repair proteins, and microsatellite instability) should be performed at the latest when progression from the hormone-sensitive to the castration-resistant phase is imminent (*20*).

NMCRPC

In cases of PSA progression and in the absence of evidence of metastases on conventional imaging, the condition is formally classified as nmCRPC. A PSA level of at least 2 μg/L and a PSA doubling time of no more than 10 mo are associated with a poor prognosis and an increased risk of metastases (*36*). Three large studies (ARAMIS, PROSPER, and SPARTAN) have demonstrated a statistically significant prolongation of both rPFS and OS through the early use of an ARPI (apalutamide, darolutamide, enzalutamide) (*4–6*). It is important to emphasize in this context that modern imaging with PSMA PET was not used in the 3 studies mentioned. The concept of nmCRPC is an artificial one that is seen when high-risk patients are evaluated using PSMA PET, because evidence of metastases (including locoregional and distant metastases) can be found in more than 90% of patients but may not have been recognized as such on conventional imaging because of its lower accuracy (*37*). The use of ARPI in combination with ADT in the nmCRPC setting may change the natural history of the disease and has implications on the available treatment options at progression.

POSSIBLE SEQUENCE THERAPIES IN MCRPC

Crucial to the choice of therapy in the castration-resistant situation is prior treatment. Accordingly, different scenarios are listed and discussed separately. Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org) summarizes the available treatments (*38*).

The studies PROpel, MAGNITUDE, and TALAPRO-2 have investigated the benefit of ARPI plus poly(adenosine diphosphate ribose) polymerase (PARP) inhibitor combination therapy in the first-line mCRPC setting. (*39–41*). Preclinically, there is evidence of a synergistic effect between PARP inhibition and ARPI. However, clinical studies show that patients with BRCA mutations benefit most from the combination (*39–41*). Combination therapy has less of an effect in patients with other HRR alterations, and data for patients without HRR alterations have been controversially discussed. A significant OS benefit has yet to be demonstrated in any study at the time of writing.

It is also important to note that most patients included in the 3 studies had previously received only ADT as treatment; only 20%–30% received docetaxel in the mHSPC situation, and less than 10% received an ARPI. The use of a PARP inhibitor is associated with significant, primarily hematologic, toxicity. In all 3 studies, many patients had to interrupt therapy (≤75%), reduce the PARP inhibitor dose (≤50%), or even discontinue PARP inhibitor therapy (≤20%). Regulatory authorities interpret the data differently. The Food and Drug Administration has approved the combinations for patients with BRCA alteration (niraparib plus abiraterone and olaparib plus abiraterone) and for patients with HRR alterations including BRCA (talazoparib plus enzalutamide). Similarly to the Food and Drug Administration, the European Medicines Agency has approved the combination of niraparib plus abiraterone only for patients with BRCA alteration, whereas the other 2 combinations (olaparib plus abiraterone and talazoparib plus enzalutamide) have been approved for all patients with mCRPC regardless of mutation status when chemotherapy is not indicated.

TREATMENT OPTIONS AFTER ADT ALONE OR ADT PLUS DOCETAXEL FOR MHSPC

This situation will become less common because of the increased use of ADT-plus-ARPI combination therapies in mHSPC. In the absence of molecular alterations, an ARPI is primarily considered in this situation. A consensus was reached on this at the APCCC 2024 consensus conference (Supplemental Table 2) (*19*).

There is strong evidence from 2 phase III studies for abiraterone and enzalutamide (*3*). In these pivotal studies (PREVAIL and COU-302), only patients with asymptomatic or minimally symptomatic disease were included, and no chemotherapy pretreatment was allowed. Patients with visceral metastases or a low PSA level relative to the extent of metastasis should be closely monitored for early detection of disease progression. A valid alternative, especially in patients with unfavorable prognostic factors, could be cabazitaxel since in the TROPIC trial, cabazitaxel was shown to improve OS compared with mitoxantrone in patients with mCRPC progressing after docetaxel (*3*).

Data presented at the European Society for Medical Oncology meeting on the PEACE-3 trial showed a significant improvement in rPFS for the first-line mCRPC combination of ^{223}Ra plus enzalutamide in patients with asymptomatic or mildly symptomatic bone-predominant metastases (*42*). About 30% of the included patients had received prior docetaxel, and very few patients (<3%) had received abiraterone for mHSPC. The study met its primary endpoint: enzalutamide plus ^{223}Ra improved rPFS compared with placebo (hazard ratio, 0.69; 95% CI, 0.54–0.87). With 80% of events achieved, the combination therapy was shown to also improve OS in the log-rank test (0.69; 95% CI, 0.52–0.90); however, this study has not been published yet, and recommendations should therefore be given only after formal publication of the results. The use of a bone-protecting agent has been mandatory during the trial, resulting in a drastic reduction in the number of bone fractures in both arms (*43*). This confirms the importance, already at the start, of adding a bone-protecting agent in most patients at the start of ADT for prevention of cancer treatment–related bone loss and, more lately, in the setting of mCRPC with bone metastases to reduce the risk of skeleton-related events independently of the treatment given. The combination of enzalutamide plus ^{223}Ra may be an option for patients with mCRPC and

bone metastases who have received only ADT or ADT plus docetaxel in the mHSPC situation.

With the identification of a pathogenic BRCA alteration, data from the 3 studies (PROpel, MAGNITUDE, and TALAPRO-2) permit the use of combination therapy (ARPI plus PARP inhibitor) (*39–41*). The control arms of the 3 studies demonstrated that patients with a BRCA alteration respond significantly less favorably to an ARPI than does the control group without such a mutation. This finding supports the use of combination therapy. A sequential approach, meaning first an additional ARPI therapy followed by the use of a PARP inhibitor on progression, could theoretically also be possible. The data from the small, randomized phase II study BRCAAway (*44*) generated interesting data on this question, showing the best PFS primarily for the combined use of abiraterone and olaparib compared with sequential use. However, with a total of only 61 treated patients across 3 study arms, these data must be interpreted cautiously.

A consensus was also reached on this subject at the APCCC 2024 consensus conference (Supplemental Table 2) (*19*).

TREATMENT OPTIONS AFTER ADT PLUS ARPI FOR MHSPC

Today, most patients in the mHSPC setting are treated with ADT plus ARPI. A direct switch of ARPI is generally not recommended. On the basis of prospective studies and data from the control arms of randomized phase III studies, a direct ARPI switch shows very low antitumor activity (*3*).

On the basis of the TAX-327 study, docetaxel is currently the standard subsequent treatment in the castration-resistant phase, although in that study the patients had not previously received an ARPI (*3*). In the absence of molecular alterations, chemotherapy with docetaxel is primarily used in this situation. A consensus was also reached on this subject at the APCCC 2024 consensus conference (Supplemental Table 2) (*19*). If chemotherapy is not possible, the use of PSMA radiopharmaceutical therapy or ^{223}Ra should be evaluated (*19*).

Data from the PSMAfore study, presented at the European Society for Medical Oncology 2023 meeting and subsequently published, demonstrated a significant advantage in rPFS for ^{177}Lu-PSMA-617 (7.4 GBq intravenously every 6 wk for ≤6 cycles) compared with ARPI switching in patients who had not yet received chemotherapy and for whom chemotherapy was not urgently indicated (median rPFS, 11.6 vs. 5.59 mo) (*45*). To date, an OS benefit has not been demonstrated in the study, partly because many patients from the control arm were able to switch to the radiopharmaceutical therapy arm on disease progression.

At the European Society for Medical Oncology 2024 meeting, the data of the phase 3 SPLASH trial were presented. This trial enrolled PSMA PET–positive patients with mCRPC who progressed on 1 ARPI and had not received chemotherapy for mCRPC. Patients were randomized to ^{177}Lu-PNT2002 (6.8 GBq intravenously every 8 wk for ≤4 cycles) or an ARPI change with a primary endpoint of rPFS. This trial also met the primary endpoint of improvement in rPFS (median rPFS, 9.5 vs. 6 mo) (*46*). Formal approval for the use of radiopharmaceutical therapy for patients with mCRPC who have not yet received chemotherapy is currently pending in many countries. It is anticipated that this treatment option will gain increasing importance in this situation over the next few years, especially with good patient selection, considering that chemotherapy remains an active treatment option after radiopharmaceutical therapy. Another phase III trial with ^{177}Lu-PNT2002 (ECLIPSE) has compared 6 doses of ^{177}Lu-PNT2002 (7.4 GBq every 6 wk) with an ARPI switch, and the data are expected to be presented soon.

For patients with a pathogenic BRCA alteration, there are various options available. There are strong data for monotherapy with PARP inhibitors (olaparib, rucaparib) (*47*,*48*). Currently, olaparib is approved only for patients with pathogenic BRCA alterations (germline or somatic). The 3 large, randomized studies (PROpel, MAGNITUDE, and TALAPRO-2) included few patients who had previously received an ARPI. Given that sequential use of ARPIs is associated with only low antitumor activity, the question arises as to whether a combined treatment with ARPI plus PARP inhibitor would be sensible for patients with progression under ADT and an ARPI. No consensus was reached on this at the APCCC 2024 meeting, but the overwhelming majority voted in favor of using a PARP inhibitor, whether as monotherapy or in combination with an ARPI (Supplemental Table 2) (*19*).

For a molecular profile associated with an increased likelihood of response to checkpoint inhibitor therapy (defective mismatch repair proteins, MSI-high), such therapy may be considered in individual cases in the mCRPC situation (*49*). The use can be justified by 2 studies showing efficacy independent of the cancer of origin, on which bases the Food and Drug Administration has approved pembrolizumab and dostarlimab (*50*,*51*).

TREATMENT OPTIONS AFTER ADT PLUS ARPI PLUS DOCETAXEL FOR MHSPC

A particular challenge in the future will be patients who have already received a triple-combination therapy (ADT plus ARPI plus docetaxel) in mHSPC. There is currently no strong evidence from prospective, randomized phase III studies for this specific patient group. Some of the considerations mentioned above also apply in this situation.

In the absence of molecular alterations, radiopharmaceutical therapy extrapolated from the VISION study could be given in this context (*52*). A prerequisite is PSMA PET imaging, which demonstrates relevant PSMA expression in all tumor manifestations. The VISION trial compared ^{177}Lu-PSMA-617 (7.4 GBq every 6 wk for 4–6 cycles) plus the protocol-permitted standard care with standard care alone. Protocol-permitted standard care excluded chemotherapy, immunotherapy, ^{223}Ra, and investigational drugs but allowed an ARPI switch, low-dose steroids, palliative RT, and osteoprotective therapy with bisphosphonates or denosumab. ^{177}Lu-PSMA-617 plus standard care significantly prolonged median rPFS (8.7 vs. 3.4 mo) and median OS (15.3 vs. 11.3 mo) and has led to the approval of the radiopharmaceutical therapy in patients with mCRPC after treatment with an ARPI and 1 line of chemotherapy.

Alternatively, cabazitaxel can be used on the basis of the TROPIC study (*3*). A direct comparison of cabazitaxel with ^{177}Lu-PSMA-617 in the TheraP trial showed a better response rate and tolerability for radiopharmaceutical therapy than was seen with cabazitaxel but no significant improvement in OS (*53*,*54*). Of note, the dose of ^{177}Lu-PSMA-617 used in the TheraP trial was higher than the dose used in VISION or PSMAfore.

Patients with symptomatic progression and evidence of metabolically active bone metastases without visceral metastases, who are not fit for chemotherapy with docetaxel, might be considered for radiopharmaceutical therapy using ^{223}Ra (*55*).

For patients with a pathogenic BRCA alteration, the considerations outlined above apply. The use of a PARP inhibitor could be an effective treatment option after pretreatment with ADT plus ARPI plus docetaxel. No consensus was reached on this at the APCCC 2024 meeting, but the overwhelming majority voted in favor of using a PARP inhibitor, whether as monotherapy or in combination with an ARPI (Supplemental Table 2) (*19*).

GENERAL CONSIDERATIONS

Currently, there is no uniform clinical, laboratory, or pathologic definition for the aggressive variant of PC. It is suspected in cases of, for example, new or extensive visceral progression, disease progression with stable or low PSA levels, or new osteolytic bone metastases. If possible, a biopsy should be performed to rule out a treatment-emergent neuroendocrine dedifferentiation or a second malignancy. The biopsy can investigate whether a dedifferentiated adenocarcinoma variant (often still showing PSA and androgen receptor expression) or a neuroendocrine differentiation (expression of synaptophysin, chromogranin A, CD56) is present. The biopsy material may also be useful for further molecular pathologic investigations. In case of diagnosis of aggressive-variant PC, an intensified treatment such as cabazitaxel plus carboplatin could be considered according to the data of the phase I/II study by Corn et al. (*56*).

Low platelets can be side effect of treatment (mostly chemotherapy or radiopharmaceutical therapy) but also a sign of disease progression in the sense of development of a disseminated intravascular coagulation or progressing bone marrow infiltration. Therefore, patients with thrombocytopenia have to be followed up closely and evaluated to rule out reasons other than a side effect of the treatment.

Furthermore, as recommended by international guidelines, patients with mCRPC and bone metastases should receive a bone-protecting agent (denosumab or zoledronic acid monthly) in the absence of contraindications to reduce the risk of skeleton-related events (*20*,*21*,*57*,*58*). Even in patients with hormone-sensitive disease who start long-term ADT with or without ARPI, bone health should be carefully considered, introducing calcium and vitamin D supplementation and evaluating the introduction of a bone-protecting agent to reduce ADT-related bone loss (*59*).

CONCLUSION

For patients with mCRPC, various treatment options are available. These include ARPI (abiraterone and enzalutamide), chemotherapy (docetaxel and cabazitaxel), PARP inhibitor (monotherapy or in combination with an ARPI), and radiopharmaceutical therapy (^{223}Ra and ^{177}Lu-PSMA). PSMA radiopharmaceutical therapy, in particular, might in the future be used in early disease settings (awaiting the results of ongoing studies). However, several questions remain regarding this treatment. Which patients can benefit most from this therapy? How does one choose between the various PSMA radioligand molecules (^{177}Lu-PSMA I&T vs. ^{177}Lu-PSMA 617)? What is the ideal dose, scheduling, and timing of these therapies? Therefore, it appears of fundamental importance to establish an even closer collaboration between oncologists and nuclear medicine physicians and, ideally, the presence of a specialist nuclear medicine physician on multidisciplinary tumor boards.

An optimal therapy sequence cannot currently be defined; the treatment sequence is based on the individual extent of the disease, existing symptoms, comorbidities, medications, and previously administered therapies. Closely monitoring patients with mCRPC is essential to not lose the opportunity to switch to another active therapy when the current one no longer works. For this reason, regular imaging should be performed, and when PSMA PET CT is used, the CT part should be done with contrast medium so as not to miss PSMA-negative progression.

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