Journal of Bone and Mineral Metabolism (2023) 41:317–326
https://doi.org/10.1007/s00774-023-01435-w

INVITED REVIEW

Management of bone metastasis in prostate cancer

Kazuo Nishimura[1]

Received: 29 September 2022 / Accepted: 18 April 2023 / Published online: 10 May 2023

Abstract
Progression of bone metastases is the primary cause of death in prostate cancer, and skeletal-related events (SREs), including pathologic fractures, spinal cord compression, radiation, or surgery to bone can impair patients' quality of life. Over the past decade, the development of cytotoxic agents, androgen-receptor-axis-targeted therapies (ARATs), and radioligand therapies has prolonged overall survival of prostate cancer patients with bone metastases and reduced the risk of SREs. The use of bone-modifying agents has also contributed to the reduced risk of SREs. Initial use of a cytotoxic agent, docetaxel, or an ARAT agent with androgen deprivation therapy (ADT) is the current approach to metastatic castration-sensitive prostate cancer. However, there is no consensus on the optimal medication for upfront use in combination with ADT, or on specific patient selection. Recently, next-generation imaging modalities, such as whole-body magnetic resonance imaging and prostate-specific membrane antigen-positron emission tomography have been utilized to detect bone metastases at an early stage. In addition, metastasis-directed therapy, such as stereotactic body radiation therapy, has been attempted. In the future, patients with bone metastatic prostate cancer will be divided into subgroups and their treatment options will be tailored to their specific characteristics.

Keywords Prostate cancer · Bone metastasis · Skeletal-related event · Radium-223 · Bone-modifying agent

Introduction

Bone is the most frequent site of distant metastasis, and progression of bone metastasis is the primary cause of death in prostate cancer. Approximately 5–10% of men with newly diagnosed prostate cancer reportedly have bone metastases [1, 2], and these rates increase substantially in patients with elevated prostate-specific antigen (PSA) levels, and advanced tumor grade (Gleason Score) and local tumor (T) stage [1–3]. Accordingly, patients with PSA level 20 ng/ml or greater, Gleason score 8 or greater, or locally advanced disease are at higher risk of bone metastases and should be considered for further evaluation [2].

Androgen deprivation therapy (ADT) including castration, luteinizing hormone-releasing hormone agonists or antagonists, and anti-androgens, is the main systemic therapy used for prostate cancer with bone metastasis. However, eventually, the disease will progress from a castration-sensitive (metastatic castration-sensitive prostate cancer; mCSPC) to a castration-resistant state (metastatic castration-resistant prostate cancer; mCRPC). Since the bone is the predominant site of disease progression, the management of bone metastasis is key to the management of mCRPC.

Anatomical pattern and distribution of bone metastasis

In 1940, Batson first reported the vertebral system of veins, including the periprostatic, pelvic, paravertebral, intrathoracic, and intracranial veins, after a series of cadaver experiments using contrast liquid [4]. He described how the distribution of bone metastases from prostatic cancer follows the course of the vertebral venous system, especially veins that surround the sacrum, pelvis, and lumbar spine, and that tumor cells disseminate through the spinal veins as a result of venous reflux that occurs after an increase in intra-abdominal pressure caused by the Valsalva maneuver.

Bubendorf et al. analyzed the autopsy reports of 1589 men with prostate cancer [5], finding that the spine was the

✉ Kazuo Nishimura
kazuo.nishimura@oici.jp

[1] Department of Urology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan

most common site (90%) of metastasis. In 100 such patients with detailed information available, metastases were most common at the lumbar (97%) followed by the thoracic (66%) and cervical spine (38%). The results support Batson's proposal that the vertebral venous route is the predominant pathway of bone metastasis from prostate cancer.

Prognosis-based classification

The prognosis of patients with prostate cancer and bone metastasis is heterogenous. Patients can be simply and intuitively classified according to metastatic volume and the time of metastatic disease occurrence (synchronous vs. metachronous) [6] (Fig. 1). De Bruycker et al. assessed the patterns of recurrence after primary prostate cancer treatment (radical prostatectomy and/or radiotherapy), finding that bone metastasis accounted for 18% of all recurrences, followed by lymph node metastasis. They showed that low-volume disease recurrence (local recurrence or ≤ 3 metastases) was associated with longer time to CRPC than high-volume recurrence (≥ 4 metastases) [7].

Sridharan et al. [8] showed a clear prognostic gradient according to the number of bony metastatic sites after ADT + radiation therapy. These results have led to great interest in local therapy for oligometastasis.

In 1995, Hellman and Weichselbaum [9] proposed that oligometastatic presentation is an intermediate state of cancer spread between localized and disseminated metastatic cancer. In this state, eradication of oligometastases may be curative in some but not all patients, because these visible lesions are simply the initial manifestations of a more widespread metastatic process. Therefore, the appropriate use of diagnostic modalities to distinguish between disease states is crucial when planning definitive eradication in patients with metastatic disease, including those with prostate cancer.

Imaging studies

99mTc-bone scan

The 99mTc-bone (BS) scan is a sensitive, standard imaging method for assessing the distribution of active bone formation in the skeleton, which is associated with both malignant and benign disease. Since osteoblastic lesions are the predominant type of bone metastasis in prostate cancer, BS is commonly used to detect bone metastasis at the initial diagnosis as well as biochemical recurrence after local treatment (radical prostatectomy/radiation therapy). However, the positive scan rate is low among patients with low serum PSA levels and Gleason grades at the initial diagnosis [2]. Thus, it is recommended that BS should be avoided in patients with PSA < 2 ng/mL after radical prostatectomy [10]. At the initial post-treatment scan, there may be bone scan flares or an osteoblastic healing reaction; therefore, caution is required when used to assess therapeutic efficacy. Single photon emission computed tomography is mostly used to further elucidate the anatomy and improve the diagnostic accuracy of BS.

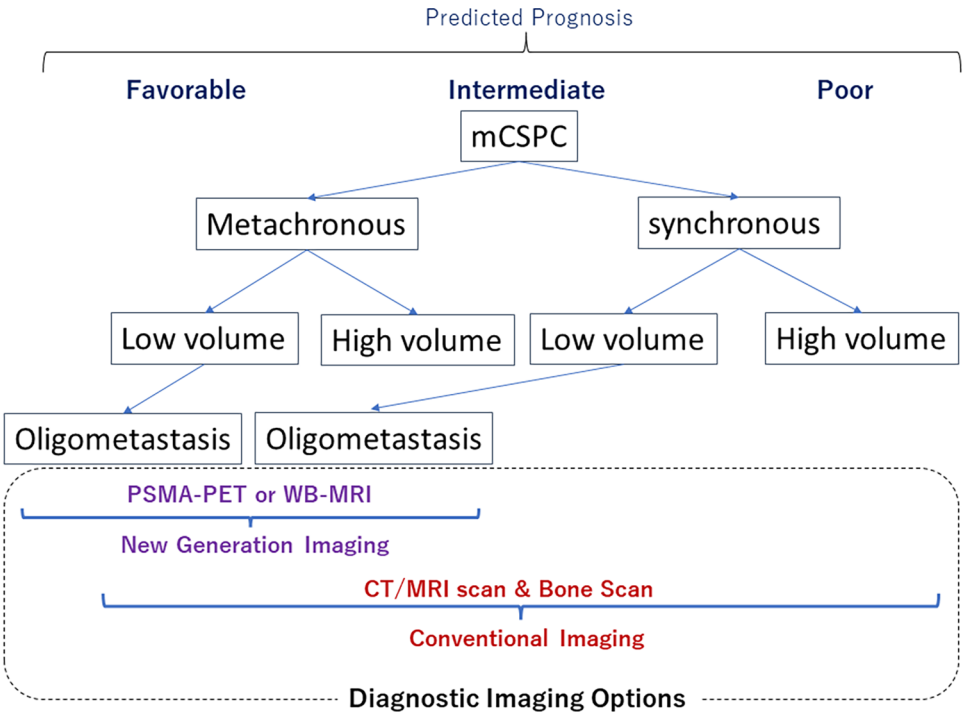

Fig. 1 Classification of metastatic castration-sensitive prostate cancer based on prognosis. *mCSPC* metastatic castration-sensitive prostate cancer, *PSMA-PET* prostate-specific membrane antigen-positron emission tomography, *WB-MRI* whole-body magnetic resonance imaging

Whole-body magnetic resonance imaging

Magnetic resonance imaging (MRI) provides excellent contrast resolution of the bone and soft tissue and helps distinguish equivocal lesions found on BS, thus achieving excellent sensitivity and specificity for detecting bone metastases [11]. While the limited field of view and long examination time were problems before the introduction of whole-body MRI (WB-MRI) [12], the development of multichannel coils and tabletop extenders has enabled whole-body scanning to be performed in a single session [13, 14]. Takahara et al. [15] adapted diffusion-weighted imaging (DWI) for WB malignancy screening and reported the utility of DWI with background body signal suppression (DWIBS) in 2004. Since their seminal report, DWIBS has been commonly performed along with WB-MRI for the detection of bone metastases from prostate cancer as well as other malignancies.

WB-MRI has been shown to be more effective than BS and computed tomography (CT) in the detection of bone metastasis from prostate cancer and the evaluation of treatment response [16]. A meta-analysis showed that WB-MRI had a similarly high specificity (99% vs. 95%) and a higher sensitivity (94% vs. 80%) for bone metastases compared to BS [17].

Prostate-specific membrane antigen-positron emission tomography

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein with folate hydrolase activity produced by the prostatic epithelium [18]. PSMA is negatively regulated by androgens, and is upregulated by many folds in prostate cancer and metastatic disease [19]. Its expression correlates with aggressive [20] as well as androgen-independent prostate cancer [19]. There is accumulating evidence of the utility of PSMA-positron emission tomography (PET) in detecting nodal and skeletal disease in prostate cancer [21, 22]. In fact, PSMA-PET has greater sensitivity and specificity for the detection of pelvic lymph node and distant metastases than CT and BS, as well as other PET tracers [23–26].

The Food and Drug Administration approved Ga-68 PSMA-11 as the first PSMA-targeted PET imaging tracer in 2020, which was followed by piflufolastat F-18 in 2021. The use of these tracers is indicated in patients with suspected prostate cancer metastasis who are potentially curable, as well as those with suspected recurrence based on elevated PSA levels. However, PSMA is reportedly be expressed in both neoplastic and non-neoplastic tissues [27]. Furthermore, tracer uptake by ganglia and unspecific uptake by bone means that caution must be exercised when interpreting PSMA-PET findings [28, 29].

Management of skeletal-related events

Skeletal-related events (SREs) are common complications associated with bone metastasis, and include pathologic fractures, spinal cord compression, radiation, or surgery to bone [30]. SREs can cause impaired quality of life and increased mortality [31]. Therefore, the prevention of SREs is critical to the management of prostate cancer patients with bone metastasis. Symptomatic SREs are those that are clinically detectable, irrespective of radiographic findings, and have been commonly employed as more relevant endpoints in recent clinical trials for prostate cancer with bone metastasis [30] (Table 1).

Bone pain

Analgesics such as opioids and nonsteroidal anti-inflammatory drugs are commonly used for bone pain. In addition, bone-modifying agents (BMAs), such as zoledronic acid, may also achieve modest improvement in pain [32].

Pain relief can be achieved by external beam radiation therapy (EBRT) to a single or limited number of painful bone metastases. The American Society for Radiation Oncology recommends single-fraction EBRT at a dose of 8 Gy, for which there is no evidence of increased acute or late toxicity [33]. Other regimens, such as 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions, may be reasonable options for patients with longer life expectancy given that they are associated with a lower incidence of retreatment [33].

Spinal cord compression

Spinal metastases may lead to spinal cord compression, which can cause pain, irreversible loss of neurologic function, and deterioration of quality of life. The natural course of spinal metastases arising from prostate cancer has changed considerably given the revolution in treatment options and timing of interventions. Spinal cord compression is an oncologic emergency requiring correct diagnosis and prompt treatment [34]. MRI of the entire spine is recommended, and immediate treatment consisting of glucocorticoids, pain management, and radiation therapy, with or without surgery, is required [34].

Risk of bone fracture

The risk of bone fracture is likely to rise with increasing age, potentially owing to increased bone loss by various mechanisms [35]. ADT can also induce loss of bone density, which can lead to osteoporotic fractures. This effect may be further exacerbated by the presence of bone

Table 1 Skeletal-related events during systemic treatment for metastatic prostate cancer

Disease status	Trials	Patients category	Treatment arms	SRE or SSRE	Evaluation	Study drug	Control	HR	*P* value
						Median (months)			
mCSPC	ARASENSE	Metachronous and synchronous mets chemo-fit	ADT + DTX + Dalo versus ADT + DTX + placebo	SSRE	Time to first SSRE	NR	NR	0.71	0.02
	LATITUDE	Synchronous mets and high risk	ADT + ABI versus ADT	SSRE	Time to SSRE	NR	NR	0.75	0.0181
	TITAN	Metachronous and synchronous mets	ADT(± DTX) + APA versus ADT(± DTX)	SSRE	Time to SSRE	NR	NR	0.86	0.361
	ARCHES	Metachronous and synchronous mets	ADT(± DTX) + ENZ versus ADT(± DTX)	SSRE	Time to first SSRE	NR	NR	0.52	0.0026
mCRPC	Zoledronic acid prostate cancer study	Bone mets	Zoledronic acid versus placeb	SRE	Time to first SRE	16	10.5	0.68	< 0.01
	Prostate cancer SRE study (NCT00321620)	Bone mets	Denosumab versus zoledronic acid	SRE	Time to first SRE	20.7	17.1	0.82	0.008
	COU-AA-301	Post-DTX	ABI + Pred versus Pred	SRE	Time to first SRE	25.0	20.3	0.615	0.0001
	AFFIRM	Post-DTX	ENZ versus placebo	SRE	Time to first SRE	16.7	13.3	0.69	*P* < 0.001
	PREVAIL	Pre-DTX, no/mild symptom	ENZ versus placebo	SRE	Time to SRE	31.1	31.3	0.72	*P* < 0.001
	ALSYMPCA	Symptomatic bone mets, no visceral mets	Ra-223 + BSC versus placebo + BSC	SSRE	Time to first SSRE	15.6	9.8	0.66	< 0.001
	ERA-223	Pre-DTX, no/mild symptom	Ra-223 + ABI versus ABI	SSRE	Time to first SSRE or death	22.3	26	1.122	0.2636
	VISION	Post-DTX/CBZ, post ARAT agent	Lut-177-PSMA + SC vs SC	SSRE	Time to first SSRE or death	11.5	6.8	0.5	< 0.001

metastases. In addition, concomitant medications, such as androgen-receptor-axis-targeted therapy (ARAT) agents abiraterone, enzalutamide, and apalutamide; and glucocorticoids, also reportedly increase the incidence of bone fractures [36–40]. Abiraterone blocks the synthesis of testosterone, and thus needs to be used with glucocorticoids. Meanwhile, enzalutamide and apalutamide inhibit androgen receptor activity, which may interfere with the bone-protecting effect of androgens. They are also associated with central nervous system toxicities, leading to falls and traumatic fractures (Table 2).

Bone-modifying agents

The role of BMAs, such as zoledronic acid and denosumab, in reducing the incidence of SREs as well as delaying their onset in patients with bone metastases from prostate cancer has been well characterized. The results from clinical trials support their use for patients with bone metastasis in mCRPC setting [32]. The ALLIANCE 90202 trial found that zoledronic acid use in men with mCSPC was not associated with reduced risk of SREs [41]. A phase III trial compared denosumab and zoledronic acid among patients with

Table 2 Androgen-receptor-axis-targeted therapy agents and risk of bone fracture

Disease status	Clinical trial	Study arm agent	Control arm agent	All grade bone fracture (%)		Published year
				Study arm	Control arm	
mCSPC	ARCHES	Enzalutamide	Placebo	6.5	4.2	2019
mCSPC	TITAN	Apalutamide	Placebo	6.3	4.6	2019
m0CRPC	PROSPER	Enzalutamide	Placebo	17*	8*	2018
m0CRPC	SPARTAN	Apalutamide	Placebo	11.7	6.5	2018
m0CRPC	ARAMIS	Darolutamide	Placebo	4.2	3.6	2019
mCRPC	TERRAIN	Enzalutamide	Bicalutamide	3	1	2016

mCSPC metastatic castration-sensitive prostate cancer, *m0CRPC* non-metastatic castration-resistant prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer

*Fall and nonpathologic fracture

mCRPC and bone metastasis [42]. The results showed that denosumab was superior for the prevention of SREs (median time to first SRE 20.7 months vs. 17.1 months; hazard ratio: 0.82; $p = 0.008$), but there was no difference in overall survival and time to disease progression. Regarding adverse events, hypocalcemia occurred more frequently in the denosumab arm (13% vs. 6%; $p < 0.0001$), while osteonecrosis of the jaw (ONJ) was infrequent in both arms (2% vs. 1%).

The standard doses are 120 mg subcutaneous denosumab every 4 weeks, and 4 mg intravenous zoledronic acid every 3–4 weeks, which is consistent with the guidelines from Cancer Care Ontario and the American Society of Clinical Oncology [32]; however, the optimal duration for safe administration of BMAs has not been established. The incidence of ONJ has been shown to increase with longer exposure to BMAs [43]. A retrospective study of patients with prostate cancer and bone metastasis showed that the 2-year ONJ incidence rate was 8.9%, and low serum calcium, use of chemotherapeutic agents, and use of denosumab were possible risk factors [44].

There are data supporting the administration of zoledronic acid every 12 rather than every 4 weeks [45]. Thus, prolonging the interval of BMAs may help avoid the risk of ONJ without compromising SRE prevention. More importantly, a dental check-up is essential prior to the start of BMA because poor oral hygiene and invasive dental treatment are common predisposing factors for ONJ [46].

Radiation therapy to oligometastatic disease in prostate cancer

There have been no large randomized controlled trials focused on radiotherapy to metastatic disease, and no consensus has been reached on its efficacy. Meanwhile, retrospective and single-arm studies have reported its effectiveness, including delayed progression and initiation of ADT [47, 48]. Stereotactic body radiotherapy (SBRT) is a newly introduced approach that has helped improve treatment efficacy while reducing treatment-associated adverse events.

The efficacy of metastasis-directed therapy (radiation therapy/metastasectomy) in recurrent, metachronous oligometastatic CSPC after curative treatment has been demonstrated in two randomized phase II trials [49, 50]. The STOMP trial in Europe evaluated the efficacy of SBRT for 1 to 3 recurrent metastatic lesions, and showed an improved median ADT-free survival of 21 months compared with 13 months in the surveillance group [49]. The ORIOLE study in the U.S. showed that PSA progression at 6 months was 19% in the SBRT group compared to 61% in the follow-up group, indicating significant improvement (median progression-free survival: not reached vs. 5.8 months; hazard ratio: 0.30; $p = 0.002$) [50].

Radium-223

Radium-223 (Ra-223) is a radioisotope that emits α particles with a physical half-life of 11.43 days. It accumulates in areas of intense bone metabolism, replacing calcium. The α particles of Ra-223 have a very short range, about 0.1 mm, which has little effect on surrounding tissues, especially the bone marrow [51]. Ra-223 may induce DNA double-strand breaks not only in cancer cells, but also in osteoblasts and osteoclasts [52]. Therefore, it is not effective against soft tissue lesions such as lymph node and visceral metastases.

Ra-223 showed clinical benefits over placebo in patients with CRPC and bone metastases in terms of both overall survival (median, 14.9 months vs. 11.3 months) and time to first symptomatic SRE (median, 15.6 months vs. 9.8 months) in the phase III ALSYMPCA trial [53, 54]. However, Ra-223 was associated with a slightly higher frequency of G4 hematologic adverse events than placebo (anemia, 2% vs. 1%; thrombocytopenia, 3% vs. < 1%; neutropenia, 1% vs. 0%). Ra-223 is administered in 6 injections at 4-week intervals, at a dose of 55 kBq per kg body weight. Indications for

introduction of Ra-223 are CRPC with bone metastasis, absence of visceral disease, and preserved bone marrow function [53].

The ERA-223 trial compared concurrent abiraterone and Ra-223 with abiraterone alone [55] in patients at an earlier stage of CRPC with bone metastasis than those in the ALSYMPCA trial. The addition of Ra-223 to abiraterone did not improve symptomatic SREs and overall survival rates, but rather increased the risk of clinical fractures compared with abiraterone alone. Thus, concurrent use of abiraterone and Ra-223 is not recommended. Another new hormonal agent, enzalutamide, is similarly being evaluated in combination with Ra-223 in the PEACEIII trial (NCT02194248). Although the final results have not been published yet, the bone fracture rate was improved following a protocol amendment mandating the use of a BMA [56].

The optimal timing, sequence, and combination of Ra-223 with other agents remain undetermined. In the European Union, Ra-223 is indicated for use after at least two prior lines of systemic therapy for mCRPC or for patients who are ineligible for other systemic treatments [57]. The National Comprehensive Cancer Network guideline (Version 4.2022) [58] gives a category 1 recommendation for Ra-223 in symptomatic bone metastasis, regardless of its timing with respect to docetaxel or novel hormone therapy agents. An analysis of the early access to Ra-223 program showed a longer overall survival in the cohort with no or minimal pain and/or PS0 than in that with moderate or severe pain and/or PS1-2 [59]. Yamamoto et al. [60] reported that a short PSA-doubling time (< 3 months), a greater volume of bone metastases (≥ 20), and later use of Ra-223 (as 4th–5th line of treatment) are poor prognostic factors. Thus, some patients in the earlier stages of mCRPC may still benefit from Ra-223.

Radioligand therapy with 177Lu-PSMA

Several radioligands of PSMA have been developed such as 177-Lu-PSMA-617 and 177-Lu-PSMA-I&T as beta particle emitters. According to a systematic review and meta-analysis [61], PSA decline of > 50% was observed in approximately 30–70% of patients treated with these radioligands, and the median overall survival was 13.7 months. The most frequent toxicities were myelosuppression, nephrotoxicity, and salivary gland toxicity (dry mouth), most of which were mild.

In the VISION trial [62], 831 patients underwent randomization in a 2:1 ratio to receive either 177Lu-PSMA-617 plus standard care or standard care alone. All patients had PSMA-avid mCRPC and had been previously treated with one to two taxanes and an ARAT agent. 177-Lu-PSMA-617 significantly improved median radiographic progression-free survival (8.7 months vs. 3.4 months), median overall survival (15.3 months vs. 11.3 months), and median time to first symptomatic skeletal event (11.5 months vs. 6.8 months). Most adverse events observed in the 177Lu-PSMA-617 group were of grade 1 or 2.

The TheraP trial [63] compared 177-Lu-PSMA-617 with cabazitaxel in men with mCRPC who had previously received ARAT and docetaxel.177-Lu-PSMA-617 achieved superior rates of ≥ 50% PSA decline (66% vs. 37%) and pain response (60% vs. 43%) compared with cabazitaxel. Overall survival was similar with both therapies [64]. Further studies are being conducted to determine which patients are candidates for 177-Lu-PSMA therapy [65, 66].

Systemic therapy

Conventionally, the main component of systemic therapy for CSPC with bone metastasis has been ADT with or without vintage anti-androgens, such as bicalutamide or flutamide. However, the tumor will eventually progress to mCRPC, where androgen receptor axis signaling is reactivated and induces further progression (Fig. 2). Docetaxel or the novel ARATs abiraterone and enzalutamide were originally developed for this population and have shown a survival benefit [67–69]. Furthermore, cabazitaxel has demonstrated a survival benefit in patients with mCRPC who had received docetaxel [70].

Over the past 5 years, ADT plus docetaxel or a novel ARAT, including abiraterone, enzalutamide, and apalutamide, have shown improved clinical outcomes over ADT alone in patients with mCSPC [71–73]. However, there is no consensus on the optimal treatment choice among abiraterone, enzalutamide, and apalutamide. Furthermore, recent clinical trials have shown that the addition of an ARAT (abiraterone or darolutamide) to ADT plus docetaxel (triplet therapy) achieves longer survival than ADT plus docetaxel in patients with mCSPC [74, 75]. Although these trials showed the superiority of triplet therapy over ADT plus docetaxel, its superiority to ADT plus an ARAT, and which mCSPC patients would benefit the most from it remains unclear. Given that mCSPC eventually progresses to mCRPC in most patients, determining the optimal treatment sequence will be the most significant challenge in the future.

Conclusion

The life expectancy of patients with prostate cancer and bone metastasis has been prolonged owing to the development of a variety of systemic therapies. During the therapies, maintaining bone health is an essential part for preserving QOL of the patients. In the future, metastasis-directed therapy will be applied for selected patients with oligometastatic

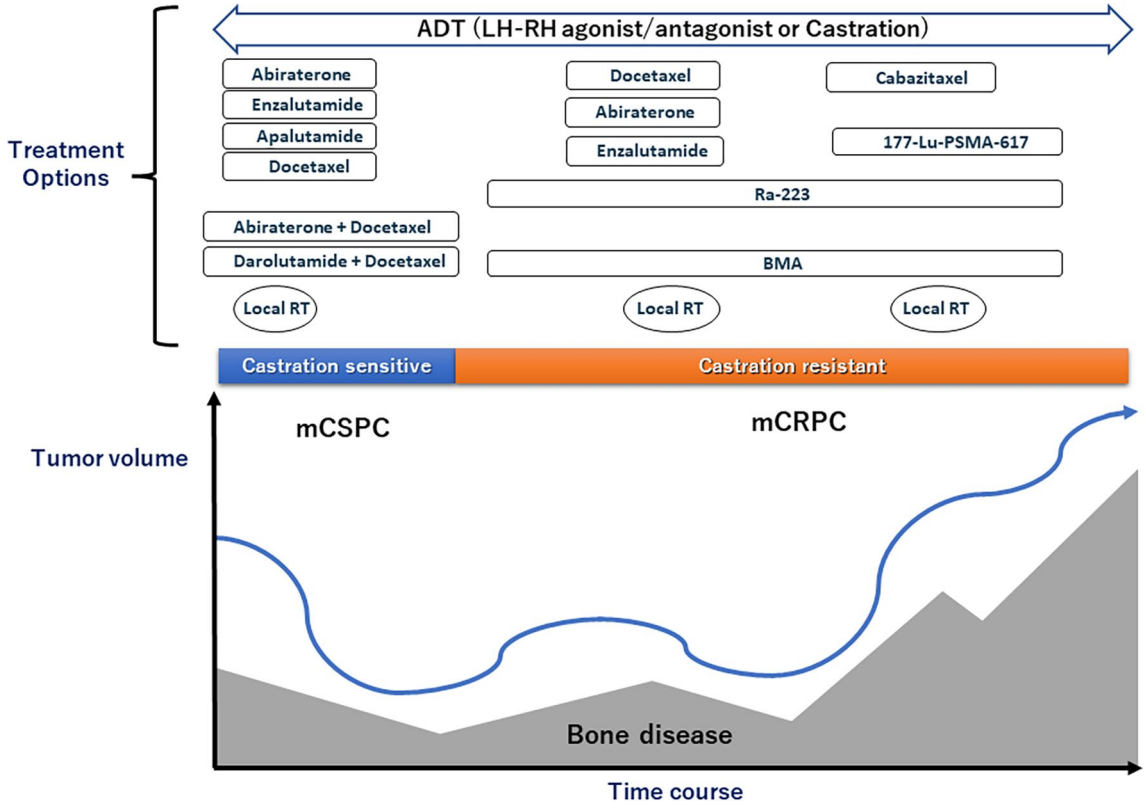

Fig. 2 Progression of prostate cancer with bone metastasis and treatment options. *ADT* androgen deprivation therapy, *LH-RH* luteinizing hormone-releasing hormone, *177-Lu-PSMA-617* 177-lutetium prostate-specific membrane antigen-617, *BMA* bone-modifying agent, *RT* radiation therapy

bone disease by the utility of new imaging techniques such as WB-MRI and PSMA-PET.

Funding None.

Declarations

Conflict of interest Dr. Nishimura has received speaker honoraria from Astellas, AstraZeneca, and Bayer; in addition to research funding from Bayer outside the submitted work.

Approval of the research protocol by an Institutional Review Board Not applicable.

Informed consent Not applicable.

Registry and the registration no. of the study/trial Not applicable.

Animal study Not applicable.

References

1. Ottosson F, Baco E, Lauritzen PM, Rud E (2021) The prevalence and locations of bone metastases using whole-body MRI in treatment-naïve intermediate- and high-risk prostate cancer. Eur Radiol 31:2747–2753. https://doi.org/10.1007/s00330-020-07363-x
2. Abuzallouf S, Dayes I, Lukka H (2004) Baseline staging of newly diagnosed prostate cancer: a summary of the literature. J Urol 171:2122–2127. https://doi.org/10.1097/01.ju.0000123981.03084.06
3. Lin Y, Mao Q, Chen B, Wang L, Liu B, Zheng X, Xie L (2017) When to perform bone scintigraphy in patients with newly diagnosed prostate cancer? A retrospective study. BMC Urol 17:41. https://doi.org/10.1186/s12894-017-0229-z
4. Batson OV (1940) The function of the vertebral veins and their role in the spread of metastases. Ann Surg 112:138–149. https://doi.org/10.1097/00000658-194007000-00016
5. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC, Mihatsch MJ (2000) Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 31:578–583. https://doi.org/10.1053/hp.2000.6698
6. Francini E, Gray KP, Xie W, Shaw GK, Valença L, Bernard B, Albiges L, Harshman LC, Kantoff PW, Taplin ME, Sweeney CJ (2018) Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate 78:889–895. https://doi.org/10.1002/pros.23645
7. De Bruycker A, Lambert B, Claeys T, Delrue L, Mbah C, De Meerleer G, Villeirs G, De Vos F, De Man K, Decaestecker K, Fonteyne V, Lumen N, Ameye F, Billiet I, Joniau S, Vanhaverbeke F, Duthoy W, Ost P (2017) Prevalence and prognosis of

low-volume, oligorecurrent, hormone-sensitive prostate cancer amenable to lesion ablative therapy. BJU Int 120:815–821. https://doi.org/10.1111/bju.13938
8. Sridharan S, Steigler A, Spry NA, Joseph D, Lamb DS, Matthews JH, Atkinson C, Tai KH, Duchesne G, Christie D, Attia J, Holliday EG, Denham JW (2016) Oligometastatic bone disease in prostate cancer patients treated on the TROG 03.04 RADAR trial. Radiother Oncol 121:98–102. https://doi.org/10.1016/j.radonc.2016.07.021
9. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13:8–10. https://doi.org/10.1200/JCO.1995.13.1.8
10. Lee CT, Oesterling JE (1997) Using prostate-specific antigen to eliminate the staging radionuclide bone scan. Urol Clin North Am 24:389–394. https://doi.org/10.1016/s0094-0143(05)70385-2
11. EAU guidelines 2022 Prostate Cancer In. https://uroweb.org/guidelines/prostate-cancer
12. Shibata H, Kato S, Sekine I, Abe K, Araki N et al (2016) Diagnosis and treatment of bone metastasis: comprehensive guideline of the Japanese Society of Medical Oncology, Japanese orthopedic association, Japanese Urological Association, and Japanese Society for Radiation Oncology. ESMO Open 1:e000037
13. Nakanishi K, Kobayashi M, Takahashi S, Nakata S, Kyakuno M, Nakaguchi K, Nakamura H (2005) Whole body MRI for detecting metastatic bone tumor: comparison with bone scintigrams. Magn Reson Med Sci 4:11–17. https://doi.org/10.2463/mrms.4.11
14. Lauenstein TC, Freudenberg LS, Goehde SC, Ruehm SG, Goyen M, Bosk S, Debatin JF, Barkhausen J (2002) Whole-body MRI using a rolling table platform for the detection of bone metastases. Eur Radiol 12:2091–2099. https://doi.org/10.1007/s00330-002-1344-z
15. Takahara T, Imai Y, Yamashita T, Yasuda S, Nasu S, Van Cauteren M (2004) Diffusion weighted whole body imaging with background body signal suppression (DWIBS): technical improvement using free breathing, STIR and high resolution 3D display. Radiat Med 22:275–282
16. Van Nieuwenhove S, Van Damme J, Padhani AR, Vandecaveye V, Tombal B, Wuts J, Pasoglou V, Lecouvet FE (2022) Whole-body magnetic resonance imaging for prostate cancer assessment: current status and future directions. J Magn Reson Imaging 55:653–680. https://doi.org/10.1002/jmri.27485
17. Sun G, Zhang YX, Liu F, Tu N (2020) Whole-body magnetic resonance imaging is superior to skeletal scintigraphy for the detection of bone metastatic tumors: a meta-analysis. Eur Rev Med Pharmacol Sci 24:7240–7252. https://doi.org/10.26355/eurrev_202007_21879
18. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C (1997) Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 3:81–85
19. Ghosh A, Heston WD (2004) Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem 91:528–539. https://doi.org/10.1002/jcb.10661
20. Bravaccini S, Puccetti M, Bocchini M, Ravaioli S, Celli M, Scarpi E, De Giorgi U, Tumedei MM, Raulli G, Cardinale L, Paganelli G (2018) PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis. Sci rep Sci Rep 8:4254. https://doi.org/10.1038/s41598-018-22594-1
21. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I et al (2020) Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 395:1208–1216. https://doi.org/10.1016/S0140-6736(20)30314-7. (**Epub Mar 22 2020**)
22. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, Saperstein L, Preston MA, Alva AS, Patnaik A, Durack JC, Stambler N, Lin T, Jensen J, Wong V, Siegel BA, Morris MJ (2021) A Phase 2/3 Prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with 18F-DCFPyL in prostate cancer patients (OSPREY). J Urol 206:52–61. https://doi.org/10.1097/JU.0000000000001698. (**Epub Feb 26 2021**)
23. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, Bolton D, Lawrentschuk N (2016) Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 70:926–937. https://doi.org/10.1016/j.eururo.2016.06.021. (**Epub Jun 28 2016**)
24. Evans JD, Jethwa KR, Ost P, Williams S, Kwon ED, Lowe VJ, Davis BJ (2018) Prostate cancer-specific PET radiotracers: a review on the clinical utility in recurrent disease. Pract Radiat Oncol 8:28–39. https://doi.org/10.1016/j.prro.2017.07.011. (**Epub Jul 20 2017**)
25. von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G (2018) 68Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography for prostate cancer: a systematic review and meta-analysis. Eur Urol Focus 4:686–693. https://doi.org/10.1016/j.euf.2016.11.002. (**Epub Nov 15 2016**)
26. Calais J, Ceci F, Eiber M, Hope TA, Hofman MS et al (2019) 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 20:1286–1294. https://doi.org/10.1016/S1470-2045(19)30415-2. (**Epub Jul 30 2019**)
27. Van de Wiele C, Sathekge M, de Spiegeleer B, De Jonghe PJ, Debruyne PR, Borms M, Beels L, Maes A (2020) PSMA expression on neovasculature of solid tumors. Histol Histopathol 35:919–927. https://doi.org/10.14670/HH-18-215
28. Rischpler C, Beck TI, Okamoto S, Schlitter AM, Knorr K, Schwaiger M, Gschwend J, Maurer T, Meyer PT, Eiber M (2018) 68Ga-PSMA-HBED-CC uptake in cervical, celiac and sacral ganglia as an important pitfall in prostate cancer PET imaging. J Nucl Med 59:1406–1411. https://doi.org/10.2967/jnumed.117.204677
29. Vollnberg B, Alberts I, Genitsch V, Rominger A, Afshar-Oromieh A (2022) Assessment of malignancy and PSMA expression of uncertain bone foci in [18F]PSMA-1007 PET/CT for prostate cancer-a single-centre experience of PET-guided biopsies. Eur J Nucl Med Mol Imaging 49:3910–3916. https://doi.org/10.1007/s00259-022-05745-5
30. Smith MR, Coleman RE, Klotz L, Pittman K, Milecki P, Ng S, Chi KN, Balakumaran A, Wei R, Wang H, Braun A, Fizazi K (2015) Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events. Ann Oncol 26:368–374. https://doi.org/10.1093/annonc/mdu519
31. Sathiakumar N, Delzell E, Morrisey MA, Falkson C, Yong M, Chia V, Blackburn J, Arora T, Kilgore ML (2011) Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US medicare beneficiaries, 1999–2006. Prostate Cancer Prostatic Dis 14:177–183. https://doi.org/10.1038/pcan.2011.7
32. Saylor PJ, Rumble RB, Tagawa S, Eastham JA, Finelli A, Reddy PS, Kungel TM, Nissenberg MG, Michalski JM (2020) Bone health and bone-targeted therapies for prostate cancer: ASCO endorsement of a cancer care Ontario guideline. J Clin Oncol 38:1736–1743. https://doi.org/10.1200/JCO.19.03148
33. Lutz PS, Balboni T, Jones J, Lo S, Petit J, Rich SE, Wong R, Hahn C (2017) Palliative radiation therapy for bone metastases: update of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol 7:4 (**Epub 2016 Aug 5**)
34. Lawton AJ, Lee KA, Cheville AL, Ferrone ML, Rades D, Balboni TA, Abrahm JL (2019) Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary

review. J Clin Oncol 37:61–71. https://doi.org/10.1200/JCO.2018.78.1211
35. Frost HM (1997) On our age-related bone loss: insights from a new paradigm. J Bone Miner Res 12:1539–1546. https://doi.org/10.1359/jbmr.1997.12.10.1539
36. Janssen Biotech, Inc (2018) Zytiga (abiraterone acetate) [prescribing information]. http://www.zytiga.com
37. Astellas Pharma US, Inc (2018) Xtandi (enzalutamide) [prescribing information]. http://www.xtandi.com
38. Janssen (2018) Products. Erleada (apalutamide) [prescribing information]. http://www.erleada.com
39. Ndibe C, Wang CG, Sonpavde G (2015) Corticosteroids in the management of prostate cancer: a critical review. Curr Treat Options Oncol 16:6. https://doi.org/10.1007/s11864-014-0320-6
40. van Staa TP, Leufkens HGM, Abenhaim L, Zhang B, Cooper C (2000) Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatol (Oxf Engl) 39:1383–1389. https://doi.org/10.1093/rheumatology/39.12.1383
41. Smith MR, Halabi S, Ryan CJ, Hussain A, Vogelzang N, Stadler W, Hauke RJ, Monk JP, Saylor P, Bhoopalam N, Saad F, Sanford B, Kelly WK, Morris M, Small EJ (2014) Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol 32:1143–1150. https://doi.org/10.1200/JCO.2013.51.6500
42. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C (2011) A randomised, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in men with castration-resistant prostate cancer. Lancet 377:813–822. https://doi.org/10.1016/S0140-6736(10)62344-6
43. Smith MR, Saad F, Coleman R, Shore N, Fizazi K et al (2012) Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 379:39–46. https://doi.org/10.1016/S0140-6736(11)61226-9
44. Nakai Y, Kanaki T, Yamamoto A, Tanaka R, Yamamoto Y, Nagahara A, Nakayama M, Kakimoto KI, Ishibashi M, Nishimura K (2021) Antiresorptive agent-related osteonecrosis of the jaw in prostate cancer patients with bone metastasis treated with bone-modifying agents. J Bone Miner Metab 39:295–301. https://doi.org/10.1007/s00774-020-01151-9
45. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ, Qin R, Go RS, Grubbs SS, O'Connor T, Velasco MR, Weckstein D, O'Mara A, Loprinzi CL, Shapiro CL (2017) Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. JAMA 317:48–58. https://doi.org/10.1001/jama.2016.19425
46. Japanese Allied Committee on Osteonecrosis of the Jaw, Yoneda T, Hagino H, Sugimoto T, Ohta H, Takahashi S, Soen S, Taguchi A, Nagata T, Urade M, Shibahara T, Toyosawa S, Toyosawa S (2017) Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. J Bone Miner Metab 35:6–19. https://doi.org/10.1007/s00774-016-0810-7
47. Rogowski P, Roach M, Schmidt-Hegemann NS, Trapp C, von Bestenbostel R, Shi R, Buchner A, Stief C, Belka C, Li M (2021) Radiotherapy of oligometastatic prostate cancer: a systematic review. Radiat Oncol 16:50. https://doi.org/10.1186/s13014-021-01776-8
48. Battaglia A, De Meerleer G, Tosco L, Moris L, Van den Broeck T, Devos G, Everaerts W, Joniau S (2019) Novel insights into the management of oligometastatic prostate cancer: a comprehensive review. Eur Urol Oncol 2:174–188. https://doi.org/10.1016/j.euo.2018.09.005
49. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, Lambert B, Delrue L, Bultijnck R, Claeys T, Goetghebeur E, Villeirs G, De Man K, Ameye F, Billiet I, Joniau S, Vanhaverbeke F, De Meerleer G (2018) Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter Phase II trial. J Clin Oncol 36:446–453. https://doi.org/10.1200/JCO.2017.75.4853
50. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ et al (2020) Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE Phase 2 randomized clinical trial. JAMA Oncol 6:650–659. https://doi.org/10.1001/jamaoncol.2020.0147
51. Cheetham PJ, Petrylak DP (2012) Alpha particles as radiopharmaceuticals in the treatment of bone metastases:mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. Oncol (Williston Park) 26:341
52. Suominen MI, Fagerlund KM, Rissanen JP, Konkol YM, Morko JP, Peng Z, Alhoniemi EJ, Laine SK, Corey E, Mumberg D, Ziegelbauer K, Käkönen SM, Halleen JM, Vessella RL, Scholz A (2017) Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. Clin Cancer Res 23:4335–4346. https://doi.org/10.1158/1078-0432.CCR-16-2955
53. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM et al (2013) Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 369:213–223. https://doi.org/10.1056/NEJMoa1213755
54. Sartor O, Coleman R, Nilsson S, Heinrich D, Helle SI et al (2014) Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 15:738–746. https://doi.org/10.1016/S1470-2045(14)70183-4. (**Epub May 13 2014**)
55. Smith M, Parker C, Saad F, Miller K, Tombal B et al (2019) Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 20:408–419. https://doi.org/10.1016/S1470-2045(18)30860-X
56. Tombal BF, Loriot Y, Saad F, McDermott RS, Elliott T, Rodriguez-Vida A, Nole F, Fournier B, Collette L, Gillessen S (2019) Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE III trial comparing enzalutamide and Ra223 versus enzalutamide alone: an interim safety analysis. J Clin Oncol 37:5007. https://doi.org/10.1200/JCO.2019.37.15_suppl.5007
57. O'Sullivan JM, Carles J, Cathomas R, Gomez-Iturriaga A, Heinrich D, Kramer G, Ost P, van Oort I, Tombal B (2020) Radium-223 within the evolving treatment options for metastatic castration-resistant prostate cancer: recommendations from a European expert working group. Urol Oncol 3:455–463. https://doi.org/10.1016/j.euo.2019.02.007
58. NCCN guidelines, version 4.2022 Prostate Cancer In. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
59. Saad F, Carles J, Gillessen S, Heidenreich A, Heinrich D, Gratt J, Lévy J, Miller K, Nilsson S, Petrenciuc O, Tucci M, Wirth M, Federhofer J, O'Sullivan JM, Radium-223 International Early Access Program Investigators (2016) Radium-223 International Early Access Program Investigators:radium-223 and concomitant therapies in patients with metastatic castration—resistant prostate cancer: an international, Early access, open-label, single-arm phase 3b trial. Lancet Oncol 17:1306–1316. https://doi.org/10.1016/S1470-2045(16)30173-5
60. Yamamoto Y, Okuda Y, Kanaki T, Tanaka R, Nagahara A, Nakai Y, Nakayama M, Kakimoto KI, Nishimura K (2021) Clinical indicators for predicting prognosis after radium-223

administration in castration-resistant prostate cancer with bone metastases. Int J Clin Oncol 26:192–198. https://doi.org/10.1007/s10147-020-01776-w
61. Yadav MP, Ballal S, Sahoo RK, Dwivedi SN, Bal C (2019) Radioligand therapy with 177Lu-PSMA for metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 213:275–285. https://doi.org/10.2214/AJR.18.20845. (**Epub Apr 17 2019**)
62. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K et al (2021) Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 385:1091–1103. https://doi.org/10.1056/NEJMoa2107322
63. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM et al (2021) 177Lu. Philippine Sugar Millers Association, Lu-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 397:797–804
64. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, Pattison DA, Tan TH, Kirkwood ID, Francis RJ, Gedye C, Rutherford NK, Zhang AY, McJannett MM, Stockler MR, Williams S, Martin AJ, Davis ID (2022) TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—overall survival after median follow-up of 3 years (ANZUP 1603). Abstract. J Clin Oncol 40(16_suppl) (suppl 16; abstr 5000). https://meetings.asco.org/2022-asco-annual-meeting/14368?presentation=207021#207021 Accessed 22 Jun 2022. https://doi.org/10.1200/JCO.2022.40.16_suppl.5000
65. Gafita A, Calais J, Grogan TR, Hadaschik B, Wang H et al (2021) Nomograms to predict outcomes after 177Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. Lancet Oncol 22:1115–1125. https://doi.org/10.1016/S1470-2045(21)00274-6
66. Kuo P, Hesterman J, Rahbar K, Kendi AT, Wei XX, Fang B, Adra N, Armstrong AJ, Garje R, Michalski JM, Ghebremariam S, Brackman M, Wong C, Benson T, Vogelzang NJ (2022) [68Ga] Philippine Sugar Millers Association, GA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [177Lu] Lu-PSMA-617 in patients with mCRPC: a VISION substudy (abstract). J Clin Oncol 40(16_suppl):5002
67. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA, TAX 327 Investigators (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502–1512. https://doi.org/10.1056/NEJMoa040720
68. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S et al (2011) Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995–2005. https://doi.org/10.1056/NEJMoa1014618
69. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN et al (2012) Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 367:1187–1197. https://doi.org/10.1056/NEJMoa1207506
70. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO, Investigators TROPIC (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 376:1147–1154. https://doi.org/10.1016/S0140-6736(10)61389-X
71. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN, LATITUDE Investigators (2017) Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377:352–360. https://doi.org/10.1056/NEJMoa1704174
72. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, Alcaraz A, Alekseev B, Iguchi T, Shore ND, Rosbrook B, Sugg J, Baron B, Chen L, Stenzl A (2019) ARCHES: a randomized, Phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 37:2974–2986. https://doi.org/10.1200/JCO.19.00799
73. Chi KN, Agarwal N, Bjartell A, Chung BH, de Santana P et al (2019) Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 381:13–24. https://doi.org/10.1056/NEJMoa1903307
74. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R et al (2022) Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet 399:1695–1707. https://doi.org/10.1016/S0140-6736(22)00367-1
75. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN et al (2022) Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 386:1132–1142. https://doi.org/10.1056/NEJMoa2119115