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Review

Selective treatment de-escalation in advanced prostate cancer: have we come full circle?

Bryan Chong[1], Marniza Saad[6], Tsung Wen Chong[1], John Thng[2], Yu Guang Tan[1], Kae Jack Tay[1], Christopher Cheng[1], Po-Hung Lin[7], Jeremy Teoh[8], Peter Ka-Fung Chiu[8], Nathan Lawrentschuk[9,10], Renu Eapen[9], Declan Murphy[9,11], Johan Chan[3], Melvin L.K. Chua[4], Jeffrey Tuan[4], John Yuen[1], Ravindran Kanesvaran[3] and Kenneth Chen[1,5]

[1]Department of Urology, Singapore General Hospital, [2]Yong Loo Lin School of Medicine, National University of Singapore, [3]Division of Medical Oncology, [4]Division of Radiation Oncology, [5]Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore, Singapore, [6]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [7]Department of Urology, Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan, [8]Division of Urology, Department of Surgery, SH Ho Urology Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China, [9]Division of Surgery, Peter MacCallum Cancer Centre, [10]Department of Urology, Royal Melbourne Hospital, Melbourne, and [11]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

Compelling evidence has solidified the notion of early treatment intensification in managing patients with metastatic hormone-sensitive prostate cancer (mHSPC). Landmark trials have provided Level 1 evidence for the survival benefits achieved by combining multiple agents. The efficacy of combined therapy relies not only on how treatment is intensified but also on how it is de-escalated. This underscores the importance of tailored treatment approaches, potentially involving a reduction in therapy for specific patients, to strike a balance between the benefits of hormonal treatment and its associated adverse effects. While de-escalation of therapy in mHSPC remains challenging due to limited evidence, it is recommended for elderly or frail patients, those with poor performance status, or experiencing significant toxicity. However, for patients with excellent prostate-specific antigen responses or favourable biomarkers, decisions should be personalised, weighing the potential benefits of continued treatment against the risk of long-term side effects, using risk stratification tools where appropriate.

Keywords

individualised treatment, metastatic hormone sensitive prostate cancer, precision medicine, treatment adverse effects, treatment de-escalation

Introduction

In the last decade, there has been a shift in the treatment approach for metastatic hormone-sensitive prostate cancer (mHSPC), marked by the integration of various androgen receptor pathway inhibitors (ARPIs) alongside androgen-deprivation therapy (ADT) [1]. The introduction of ARPIs like abiraterone acetate, enzalutamide, and apalutamide, in addition to ADT, has shown overall survival (OS) benefits [2]. The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE; ClinicalTrials.gov identifier: NCT00268476) and LATITUDE (NCT01715285) trials demonstrated improved OS with ADT combined with abiraterone acetate, emphasising its efficacy over ADT alone. Similar survival benefits were seen in the TITAN study (NCT02489318) for patients with mHSPC who received apalutamide in combination with ADT. Enzalutamide also demonstrated a superior OS when combined with ADT, as seen in the ENZAMET trial (NCT02446405), further supporting the paradigm shift from ADT monotherapy towards upfront combined therapies.

Well-established data contributed by landmark trials such as the STAMPEDE and CHAARTED (NCT00309985) trials indicates a survival advantage for patients with mHSPC, in particular, those with high-volume metastases, who receive upfront chemotherapy in combination with ADT upon diagnosis. Triplet combinations involving ADT, docetaxel, with darolutamide or abiraterone were explored in ARASENS (NCT02799602) and PEACE-1 (NCT01957436), respectively, demonstrating promising survival benefits, particularly in patients with high tumour burden [3].

The overall findings suggest that combining ADT with either chemotherapy or ARPIs and in some cases both, enhances the prognosis and survival outcomes for patients with

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Table 1 Landmark trials on intensification of therapy in mHSPC.

Trial	Publication year	Agent (comparator)	FDA approval date	OS, HR (95% CI)	PFS equivalent outcome, HR (95% CI)
CHAARTED (NCT00309985)	2015	DOC + ADT (ADT)	NA	0.61 (0.47–0.80), $P < 0.001$	0.61 (0.50–0.75), $P < 0.001$
STAMPEDE (Arm C) (NCT00268476)	2016	DOC + ADT (ADT)	NA	0.78 (0.66–0.93), $P = 0.006$	0.61 (0.53–0.70), $P < 0.001$
LATITUDE (NCT01715285)	2017	AAP + ADT (placebo + ADT)	7 February 2018	0.62 (0.51–0.76), $P < 0.001$	0.47 (0.39–0.55), $P < 0.001$
STAMPEDE (Arm G) (NCT00268476)	2017	AAP + ADT (ADT)	7 February 2018	0.63 (0.52–0.76), $P < 0.001$	0.29 (0.25–0.34), $P < 0.001$
ARCHES (NCT02677896)	2019	ENZ + ADT (placebo + ADT)	16 December 2019	0.66 (0.53–0.81), $P < 0.001$	0.63 (0.52–0.76), $P < 0.001$
ENZAMET (NCT02446405)	2019	ENZ + ADT (NSAA + ADT)	16 December 2019	0.67 (0.52–0.86), $P = 0.002$	0.39 (0.33–0.47), $P < 0.001$
TITAN (NCT02489318)	2019	APA + ADT (placebo + ADT)	17 September 2019	0.67 (0.51–0.89), $P = 0.005$	0.48 (0.39–0.60), $P < 0.001$

AAP, abiraterone acetate plus prednisolone; DOC, docetaxel; ENZ, enzalutamide; FDA, United States Food and Drug Administration; HR, hazard ratio; NSAA, non-steroidal antiandrogen drug.

mHSPC (Table 1). Despite this, real-world data highlights the dismal adoption of combined therapy, despite evidence-based recommendations [4].

Rationale for De-escalation of Treatment

This compelling evidence has collectively reinforced the concept of early treatment intensification in managing patients with *de novo* mHSPC and shaped the guidelines. While real-world evidence depicts poor adoption of these evidence-based recommendations [4], we should be cognisant that treatment intensification employing multiple agents concurrently has its own set of adverse effects. This is especially important as continuous ADT has not demonstrated superiority over intermittent ADT [5]. However, existing challenges include the absence of guidelines for treatment de-escalation and the difficulty in discerning the populations that would benefit from such de-escalation. The viability of de-escalation may be contemplated following the initial phase of treatment intensification, particularly within specific patient populations. Lastly, de-escalation can help to alleviate the financial burden of medical treatment in certain patient populations [6].

Mortality and Morbidity Associated with Treatment Intensification

Androgen-deprivation therapy has been the backbone of treatment for mHSPC for decades. However, the utilisation of ADT has also been associated with increased mortality and morbidity, manifested through heightened cardiovascular events (odds ratio 2.01, 95% CI 1.90–2.13; I^2 100%) found in meta-analyses of RCTs and cohort studies [7]. It was found that the use of ADT treatment for 6 months was associated with an earlier onset of fatal myocardial infarctions in patients aged ≥65 years [8]. Other complications include osteoporosis where the prevalence more than doubles after 2 years [9] leading to increased fracture susceptibility, sarcopenia, as well as diabetes and obesity, which further increases the risk of cardiovascular events, each contributing to a diminished quality of life (QoL) [10,11]. This prompts consideration for tailored treatment approaches, potentially involving a reduction in therapy for select patients, to strike a balance between the benefits of ADT and its associated adverse effects.

Potential Candidates for De-escalation Therapy

Given the need to balance the benefits of ADT with its associated adverse effects, the universal application of de-escalation may not be appropriate, particularly for individuals requiring continuous ADT to manage disease progression. It is thus crucial to identify the specific patient profiles suitable for de-escalation. Various patient groups, distinguished by treatment response, biomarker expression, and diverse patient and disease factors, present potential candidates for de-escalation strategies that can minimise toxicity while maintaining efficacy.

The Exceptional Responders

The first group of patients that might be suitable would be the exceptional responders. Notably, prior trials have demonstrated that exceptional responders achieving undetectable PSA levels at 6–7 months exhibit a more favourable prognosis compared to those with elevated PSA levels, rendering them more suitable for intermittent ADT. Across these studies, patients initiated ADT for durations ranging from 7 to 12 months [5,11–16], and subsequent PSA measurements gauged their treatment response. The

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Southwest Oncology Group (SWOG) 9346 trial highlighted a distinction, revealing that those individuals with PSA levels >4 ng/mL after 6–7 months of ADT experienced a markedly inferior median OS of 13 months, in contrast to 44 months for those with PSA levels of 0.2–0.4 ng/mL and 75 months for those with PSA levels <0.2 ng/mL [17]. Hence, the general consensus is that only patients with PSA levels ≤4 ng/mL are deemed suitable candidates for intermittent ADT, while those with levels >4 ng/mL are advised to undergo continuous ADT for enhanced OS [18].

Patient Factors

As previously discussed, the advantages of ADT necessitate careful consideration of its associated drawbacks. A large randomised controlled trial revealed that intermittent ADT yields improvements in certain aspects of QoL, specifically erectile function ($P < 0.001$) and mental health ($P = 0.003$) at the 3-month mark, albeit not beyond [5]. Beyond the realm of enhanced QoL, individuals experiencing treatment-related toxicity should undergo de-escalation, as the detriments outweigh the benefits for this subgroup. Additional studies have shown that while intermittent ADT shows positive impacts on activity limitation, physical capacity, and sexual functioning, there is no statistically significant enhancement in terms of adverse events [11].

Another subgroup warranting consideration for treatment de-escalation comprises elderly individuals with life-limiting comorbidities. Given their higher likelihood of succumbing to other life-limiting conditions rather than prostate cancer, intermittent ADT not only stands to improve their QoL but also potentially extend their lifespan by mitigating the risk of mortality from other competing causes, such as cardiovascular disease. Lastly, patients grappling with the adverse effects of ADT, particularly those substantially impacting QoL, may also find de-escalation a viable option. By sidestepping the side effects associated with these medications, de-escalation holds the potential to enhance QoL. In a rapid review of 10 studies, Bromley et al. [19] found that enzalutamide, apalutamide, and darolutamide can be effectively given at doses lower than the standard recommended levels without compromising treatment efficacy. This paves the way for prospective randomised trials to validate the efficacy of lower-dose regimens.

Presently, despite ongoing studies and the identification of some biomarkers, a dearth of robust data persists regarding the types of patients that are most likely to benefit. This knowledge gap has hindered the formulation of guidelines for managing patients with mHSPC. Consequently, a shared decision-making framework is crucial, fostering collaboration between patients and physicians to weigh the merits and drawbacks of continuing ADT for patients with mHSPC vs opting for de-escalation to mitigate side effects that affect patients' QoL.

Disease Factors

Disease characteristics serve as valuable tools for risk-stratifying patients with mHSPC. Typically, previous trials [20–22] have categorised these patients into four subgroups, based on two primary criteria: (i) whether the metastatic disease was synchronous, identified at the initial diagnosis, or metachronous, emerging after localised disease presentation, and (ii) the volume of disease, distinguishing between high and low volumes. High-volume disease entails visceral metastases or four or more bone metastases. A network meta-analysis revealed that, in patients with high-volume disease, triple therapy may offer improved OS compared to certain doublet therapies. However, for low-volume disease, triple therapy did not appear to provide an OS benefit over any hormonal doublet therapy [23].

Analysis revealed distinct prognostic outcomes among these subgroups when managed solely with testosterone suppression. Patients with metachronous low-volume disease exhibited a favourable prognosis, with a median survival of ~8 years, whereas those with synchronous low-volume and metachronous high-volume disease demonstrated intermediate prognoses, around 5 years, and synchronous high-volume disease exhibited the poorest prognosis, approximately 3 years [20–22].

The efficacy of certain treatments, such as enzalutamide and docetaxel, exhibited varied effects across these four subgroups. Notably, individuals with metachronous low-volume disease who had not previously received docetaxel may experience the most substantial treatment effect with enzalutamide. The trial reported a 5-year OS rate exceeding 80% for those with low-volume disease (both metachronous and synchronous), while those with synchronous high-volume disease had a 5-year survival rate of ~50% [24].

Therefore, decisions regarding treatment de-escalation should consider both disease and patient factors alongside patient preferences. Shared decision-making between physicians and patients, after careful consideration of the benefits and risks of de-escalation, as well as the estimated prognosis of the disease, is paramount.

The decision to de-escalate therapy remains complex, particularly due to the limited evidence available to guide whether to maintain or reduce treatment intensity. The survival advantage of intensified treatment appears to diminish with age. Among men aged >80 years, the increase in mean survival was 3.6 months, compared to 6 months in younger patients, despite a more significant median PSA response in the older group. This observation supports the

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rationale for de-escalating treatment in older patients, particularly when they experience greater side effects and toxicity, as the overall benefit from aggressive therapy may be reduced [25]. Hence, for some groups, such as elderly or frail patients, those with poor performance status, or those experiencing significant toxicity, a clear recommendation can be made to consider de-escalation, as the risks of continued intense treatment may outweigh the benefits. However, for patients who are responding exceptionally well, such as those with excellent PSA responses or favourable biomarkers, it is difficult to reach a clear recommendation. Treatment intensity could either be maintained because they are doing well, or it could be reduced to minimise the risk of long-term side effects. At present, there is minimal evidence to fully support either approach. Risk stratification tools, including factors such as disease volume, whether metastases are synchronous or metachronous, and emerging biomarkers, offer some helpful perspectives for guidance. However, their role in determining which patients are best suited for de-escalation remains limited with the current evidence and lack of trials answering these specific questions. This highlights the need to individualise treatment and personalise the approach in real-life practice. This entails a collaborative approach between clinician and patient, weighing up the balance between maintaining treatment efficacy and improving QoL.

Choice of Agent to De-escalate

There remains a lack of conclusive evidence and biomarkers to guide the selection of agents in a de-escalation strategy in this era of combined therapy. There is a high prevalence of cardiovascular risk factors and morbidity in patients with metastatic prostate cancer and a strong association of LHRH agonist use with cardiovascular morbidity. As such, LHRH agonists have become a rational choice to withdraw. Studies have explored the cessation of the component of ADT; however, Tombal et al. [26–28] showed that the promise of less toxicity with enzalutamide monotherapy was not apparent despite an encouraging PSA response. The SPARE trial (NCT02077634), a randomised phase II study investigating LHRH-sparing therapy in patients with chemotherapy naïve, metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate plus prednisone suggested that discontinuation of ADT may not result in decreased efficacy when considering radiographic progression-free survival (rPFS) [29]. Ongoing clinical trials, such as the phase II LACOG-0415 trial (NCT02867020), which compared a combination of ADT with abiraterone acetate vs apalutamide monotherapy vs apalutamide plus abiraterone acetate and prednisone, will shed further light on these ADT-sparing approaches. While final results are pending, early outcomes indicate that combined androgen blockade may offer superior suppression of PSA levels compared to monotherapy [30].

The concept of de-escalation is not limited to the cessation of ADT. There is discussion on dose reduction as a means to reduce long-term side effects as well. Emerging data suggests that lower doses of next-generation ARPIs, in particular, abiraterone acetate when given with low-fat meal, has comparable pharmacokinetic outcomes [31–33].

Current guidelines advocate for the intensification of ADT using either docetaxel or ARPIs in patients with mHSPC. One study has identified specific patient populations that can aid in the selection of suitable candidates for treatment. In this real-world study [34], patients harbouring speckle-type poxvirus and zinc-finger protein (*SPOP*) mutations, which affect ~5% of patients with mHSPC, demonstrated a more favourable response to ADT + ARPIs compared to docetaxel when contrasted with wild-type *SPOP* individuals. Thus, the presence of *SPOP* mutation may serve as a biomarker for guiding treatment selection in patients to de-escalate to ADT and ARPIs instead of docetaxel. However, no discernible differential benefit was observed for mutation *SPOP*-positive patients treated with docetaxel compared to those with wild-type *SPOP*.

Pending further data from these trials, clinicians may cautiously consider dose reductions of hormonal agents in selected patients, particularly where toxicity or comorbidities warrant a de-escalation approach.

Future Perspectives and Ongoing Trials

Global Health Perspective

Related to the de-escalation of treatment in advanced prostate cancer is the issue of global surgical concerns of health equity and access to therapy in low- and middle-income countries (LMICs) related to high drug costs. Many patients in LMICs present with advanced or metastatic disease from the outset due to a lack of screening or treatment options for early disease. In such scenarios, ADT for disease control and palliation of symptoms is the standard initial therapy. High drug costs are a major contributor to the disparities in outcomes between high-income countries (HIC) and LMICs. The WHO 2018 report on the pricing of cancer medicines stated that 'pharmaceutical companies set prices according to their commercial goals, with a focus on extracting the maximum amount that a buyer is willing to pay for a medicine.' [35]. De-escalation strategies may also be implemented to reduce treatment cost. For example, against the backdrop of evidence supporting non-inferiority in PFS and PSA response of low-dose abiraterone acetate (250 mg) with a low-fat meal to the standard 1000 mg dosing for patients with mCRPC, substituting apalutamide with abiraterone (250 mg) and prednisolone has been shown to result in significant cost savings, with an estimated reduction of $8400 (American dollars)/month, amounting to ~$340 230

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over the course of treatment from initiation to disease progression. While actual cost savings will depend on various factors including country specific re-imbursement schemes and accessibility to generics, the strategy of de-escalation (be it dose reduction or complete cessation of a class of therapeutics) does offer benefits in terms of mitigating financial toxicity for patients [36].

Tannock et al. [37] proposed the concept of interventional pharmacoeconomics to reduce costs through dose modification and therapeutic substitution. Abiraterone given at 250 mg with breakfast showed similar efficacy as the recommended 1000 mg, representing substantial cost savings for patients [38]. A systematic analysis comparing surgical vs medical castration by OSullivan et al. [39] has shown surgical castration to be safe, feasible and efficacious with potential survival and financial benefits over medical castration. Hence, policymakers should also adopt treatment regimens tailored to the socioeconomic conditions of each country. The Lancet Commission on prostate cancer has proposed alternatives for advanced prostate cancer treatment in HIC vs LMICs across the disease spectrum from first line to subsequent relapse settings based on the availability of advanced therapies. While HIC utilise newer-generation anti-androgens, poly-(ADP-ribose)-polymerase (PARP) inhibitors, and radium-223 for relapsed disease, LMICs should rely on more cost-effective alternatives like docetaxel and generic abiraterone, with radiotherapy (RT) limited to cases with a low disease burden [40].

Ongoing Trials Investigating De-escalation Approaches (Table 2)

Currently, A-DREAM (NCT05241860) [41] an ongoing trial is investigating de-escalation strategies across various patient cohorts. One such trial targets patients with mHSPC who exhibit exceptional responses to ARPI therapy, aiming to de-escalate treatment to allow for testosterone therapy. These patients, already receiving ADT in combination with ARPI, demonstrate stable or decreasing PSA levels after 18–24 months of ADT and a minimum of 12 months of ARPI. Monitoring of these patients entails PSA assessments every 3 months, with imaging scans conducted semi-annually or more frequently if PSA levels rise. Quality-of-life assessments are conducted every 6 months to ascertain the benefits of de-escalation. The primary objective is to determine the proportion of men experiencing an 18-month treatment-free interval from therapy with eugonadal testosterone following treatment interruption.

Another phase III randomised trial [42], the European Organisation for the Research and Treatment of Cancer Genito-Urinary Cancers Group (EORTC GUCG) 2238 de-escalate is underway to explore the safety and efficacy of intermittent maximum androgen blockade in patients achieving a PSA level of <0.2 ng/mL after 6–12 months of continuous treatment, compared to the continuation of continuous treatment. In this study, PSA levels will be closely monitored, and treatment will be reinstated if PSA levels rise to >50% of the diagnostic PSA or a maximum of 5 ng/mL. The objectives of this trial are twofold: first, to ascertain the proportion of patients who do not require treatment restart and maintain their PSA levels below the threshold; and second, to demonstrate non-inferiority of survival outcomes at 3 years with intermittent therapy compared to continuous treatment. Given that enhancing QoL is a primary aim of de-escalation, the study also aims to evaluate changes in QoL following the removal of side effects. Additional endpoints include OS, time to next systemic prostate cancer therapy, the proportion of patients requiring subsequent systemic therapy at specified intervals, toxicity profiles, and assessment of treatment resource utilisation through incremental cost-effectiveness ratio analysis. This comprehensive assessment will inform the treatment landscape for mHSPC and aid in delineating suitable patient populations for de-escalation, thereby guiding healthcare resource allocation in the management of mHSPC.

The LIBERTAS trial (NCT05884398) [43] is investigating the potential of reducing hot flashes by employing a de-escalation strategy in mHSPC through intermittent ADT. Specifically, the trial examines the intermittent ADT approach alongside apalutamide monotherapy in patients with mHSPC. The primary objective is to assess whether intermittent ADT in individuals with mHSPC, who achieve a PSA level of <0.2 ng/mL after 6 months of apalutamide and ADT combined therapy, yields non-inferior rPFS. Additionally, the trial aims to evaluate the potential benefits of de-escalation by examining the reduction in hot flash burden, measured as an 18-month percentage change in severity-adjusted hot flash scores [43].

The PREDICT-RT trial (NCT04513717) [44] is underway to explore tailored treatment approaches based on genetic risk profiles in patients with prostate cancer. This study seeks to assess whether individuals with high-risk prostate cancer can be effectively managed with a 12-month course of ADT combined with RT, rather than the standard 24-month ADT + RT regimen, while maintaining non-inferior metastasis-free survival outcomes. Key endpoints in this ongoing investigation include OS, time to PSA failure or treatment restart, proportion of patients achieving failure-free survival, prostate cancer-specific mortality, testosterone levels at PSA failure, time to testosterone recovery, incidence of adverse events, and quality-of-life measures including sexual and hormonal function. This comparative analysis aims to evaluate the feasibility and efficacy of de-escalating treatment intensity in patients with high-risk prostate cancer, providing valuable insights for optimising treatment strategies in this population [44].

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Table 2 Ongoing trials investigating de-escalation approaches in mHSPC.

Trial	Year started	Phase	Intervention	Comparator	Estimated completion
A-DREAM (NCT05241860)	2022	II	Withdrawal of both ADT and ARPIs in exceptional responders and resumption of both in: • Patients with PSA ≥5 ng/mL • Radiological progression • Symptom progression	–	2033
EORTC GUCG 2238 (NCT05974774)	2024	III	Withdrawal of both ADT and ARPIs in patients with good response until significant PSA increase as per treating physician at which point patient restarts both ADT and ARPIs. Once PSA <0.2 ng/mL, treatment stops again	Continuous ADT + ARPIs	2030
LIBERTAS (NCT05884398)	2023	III	Apalutamide + intermittent ADT per protocol	Apalutamide + continuous ADT	2027
PREDICT-RT (NCT04513717)	2020	III	RT + 12 months of ADT (Arm II)	RT + 24 months of ADT (Arm I)	2033

Conclusion

The landscape of mHSPC treatment and research has undergone substantial evolution in recent years. Landmark trials have consistently demonstrated survival benefits through treatment intensification early in the disease course, incorporating ADT, ARPIs, and chemotherapy. This emphasises the importance of early treatment intensification in mHSPC management. However, the use of multiple agents for treatment intensification also brings forth its array of adverse effects. Therefore, determining when and for whom treatment de-escalation is appropriate becomes crucial to mitigate adverse effects while preserving the benefits of early treatment intensification. The optimal de-escalation strategy hinges on various factors, including patient and disease characteristics, as well as biomarkers aiding in patient selection, timing optimisation, and agent selection for de-escalation.

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Correspondence: Kenneth Chen, Department of Urology, Singapore General Hospital, 20 College Road, Academia Level 5, Singapore 169856, Singapore.
e-mail: kenneth.chen@singhealth.com.sg

Abbreviations: ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; HIC, high-income countries; LMICs, low- and middle-income countries; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; (r)PFS, (radiographic) progression-free survival; QoL, quality of life; RT, radiotherapy; *SPOP*, speckle-type poxvirus and zinc-finger protein; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

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