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Metastatic hormone-sensitive prostate cancer: How should it be treated?

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Abstract

The number of treatment options for metastatic hormone-sensitive prostate cancer has increased substantially in recent years. The classic treatment approach for these patients – androgen-deprivation therapy alone – is now considered suboptimal. Several randomized phase III clinical trials have demonstrated significant clinical benefits – including significantly better overall survival and quality of life – for treatments that combine androgen-deprivation therapy with docetaxel, abiraterone acetate, enzalutamide, apalutamide, and/or radiotherapy to the primary tumour. As a result, these approaches are now included in treatment guidelines and considered standard of care. However, the different treatment strategies have not been directly compared, and thus treatment selection remains at the discretion of the individual physician or, ideally, a multidisciplinary team. Given the range of available treatment approaches with varying toxicity profiles, treatment selection should be individualized based on the patient's clinical characteristics and preferences, which implies active patient participation in the decision-making process. In the present document, we discuss the changing landscape of the management of patients with metastatic hormone-sensitive prostate cancer in the context of several recently-published landmark randomized trials. In addition, we discuss several unresolved issues, including the optimal sequencing of systemic treatments and the incorporation of local treatment of the primary tumour and metastases.

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Core Tip: Due to advances in the treatment of metastatic hormone-sensitive prostate cancer in recent years, multiple options are now available. The emergence of androgen receptor inhibitors provides patients with an alternative to chemotherapy. Given the increasingly important role of these novel treatments, a comprehensive review of the available data is needed. In addition, there are several unresolved questions and controversies surrounding these treatments, which can only be resolved by in-depth analysis and consensus among the specialists who treat these patients.

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INTRODUCTION

In 1941, the researchers Huggins and Hodges demonstrated, for the first time, that it was possible to reduce tumour volumes in prostate cancer (PCa) and improve disease-related symptoms through orchiectomy or estrogen therapy. This important finding was later recognized with the Nobel Prize in Physiology. Since then, androgen-deprivation therapy (ADT) has been the standard therapy for patients with newly-diagnosed metastatic PCa. In most cases, ADT is achieved with luteinizing hormone-releasing hormone (LHRH) analogues (leuprorelin, goserelin, and/or triptorelin)^[1]. While the use of LHRH antagonists is less common, it may increase in the near future due to the recent development of oral LHRH antagonists (*e.g.*, relugolix)^[2].

The estimated initial response rate of the primary tumour and metastases to ADT ranges from 60% to 80%^[3,4]. However, the prognosis of patients with metastatic disease is poor. For this reason, various clinical trials have been conducted in recent years to evaluate the benefit of treatment intensification in these patients^[5,6].

Randomized trials performed in the year 2013 were mainly focused on determining the relative value of intermittent *vs* continuous ADT in selected patients^[7]. However, just a few years later, the positive results of two phase III trials, the CHAARTED trial and the multi-arm STAMPEDE trial (arm C), both of which confirmed the superiority of docetaxel plus ADT, led to a paradigm shift. Consequently, this combined treatment approach became the new standard of care in selected patients^[8,9]. In the CHAARTED trial, patients were stratified according to disease volume (high *vs* low). High-volume metastatic disease was defined as the presence of visceral metastases and/or ≥ 4 bone lesions (with at least one located outside of the vertebral column or pelvis). Patients who did not meet at least one of these two criteria were considered to have low-volume disease^[8]. This definition is important given the benefits observed in overall survival (OS) in patients with high-volume disease (CHAARTED criteria) treated with docetaxel. In fact, the main European guidelines^[10] now recommend docetaxel in these patients. However, conclusive data regarding the magnitude of effect of this treatment in patients with low-volume disease are not available^[11,12]. Despite the limitations of the CHAARTED definition, it has been subsequently used in the design of clinical studies in the same clinical setting^[13-15].

Since then, we have witnessed the successive publication of five randomized clinical trials in which classic ADT (LHRH analogues) combined with androgen receptor signaling inhibitors (ARSi) were compared to ADT alone or, in some trials, to first-generation anti-androgens^[13-17]. The positive results of those trials supporting treatment intensification (*i.e.* combination therapy) raises new questions regarding the superiority of ARSi *vs* docetaxel and how to select the most appropriate ARSi for each patient.

Abiraterone acetate was the first ARSi to demonstrate efficacy in metastatic PCa.

The findings of the LATITUDE^[16] and STAMPEDE trials (arm G)^[17] demonstrated that abiraterone acetate combined with ADT significantly reduced mortality risk while prolonging radiographic progression-free survival (rPFS). The long-term outcomes (median follow-up, 51.8 mo) of the LATITUDE trial were recently reported, confirming the initial findings of the trial and showing that 66% of patients treated with combination therapy survived at 5 years^[18]. Subsequent quality of life (QoL) and cost-effectiveness studies further supported these findings; as a result, abiraterone acetate became the first ARSi approved for the treatment of metastatic hormone-sensitive PCa (mHSPC). Although there were differences between the two trials in terms of the type of metastatic patients (high risk *de novo* PCa in LATITUDE and any metastatic or non-metastatic patient in the STAMPEDE trial), the results of both trials showed that combination therapy provided a clinical benefit in all patient profiles^[19]. However, the Food and Drug Administration (FDA) and the European Medicines Agency only approved this treatment for *de novo* high-risk patients, defined in the LATITUDE trial^[18] as patients presenting at least two of the following three characteristics: ≥ 3 bone lesions; measurable visceral disease; and Gleason score ≥ 8 . In these patients, median survival (53.3 mo) was virtually identical to that obtained with docetaxel (51.2 mo) in the CHARTEED trial^[6] in patients with high-volume disease, even though the patient profiles in those two trials differed substantially, making it difficult to directly compare the results from these two trials.

The phase III ENZAMET^[13] and ARCHES^[14] trials, both published in 2019, confirmed the value of enzalutamide in patients with mHSPC, thus supporting the use of enzalutamide plus ADT in these patients. Although the clinical profile of the patients in the two studies was similar, there were clear differences in study design (Table 1). For example, in the ENZAMET study^[13] patients were allocated to receive either enzalutamide plus ADT or first-generation antiandrogens plus ADT; by contrast, the ARCHES^[14] trial compared enzalutamide plus ADT to ADT plus placebo. Similarly, there were also differences in the primary endpoints: OS in the ENZAMET trial and rPFS in the ARCHES trial.

At a median follow-up of < 36 mo, the results of the ENZAMET trial confirmed a benefit for the study drug (improved rPFS) in all subgroups, with a 3-year OS of 80% in the enzalutamide plus ADT arm *vs* 72% in the comparison arm (ADT plus first-generation antiandrogens [bicalutamide, flutamide, or nilutamide]). Based on these results, the FDA approved enzalutamide for the treatment of mHSPC in December 2019. However, the European Medicines Agency considered that the survival data are immature and has not, therefore, added this indication to the drug label.

The TITAN^[15] study, a randomized clinical trial involving 1052 patients, confirmed the clinical utility of apalutamide, which now forms part of the therapeutic arsenal for the treatment of mHSPC. At a median follow-up of 22.7 mo, both OS and rPFS were comparable to outcomes obtained with abiraterone acetate and enzalutamide in patients with a similar clinical profile (Table 2). At 2 years of follow-up, there was a significant reduction in both mortality risk (33%) and radiographic progression (52%). Based on these data, the FDA approved treatment in June 2019, with the following indication on the drug label “in adult men for the treatment of mHSPC in combination with androgen deprivation therapy”. However, the risk groups were not specified on the drug label, in contrast to abiraterone acetate, due to the broader inclusion criteria of the TITAN trial.

With regard to ARSi in patients with low-volume disease, patients in the ARCHES and ENZAMET trials^[13,14] were stratified by disease burden (high *vs* low-volume disease, CHAARTED criteria). The findings of those trials provided further support for the potential utility of ARSi in patients with low-volume disease beyond the usual treatment indication in high-volume, high risk patients.

The optimal treatment for mHSPC remains controversial, mainly because abiraterone acetate and docetaxel yield comparable results. However, the expected regulatory approval of apalutamide and enzalutamide (pending regulatory processes in multiple regions) is likely to end this debate. Most patients diagnosed with mHSPC are asymptomatic at diagnosis, which is why it is important to maintain QoL in these patients. A recent comparison of QoL in patients in arms C (docetaxel + ADT) and G (abiraterone acetate + ADT) in the STAMPEDE trial showed better results for abiraterone acetate, especially in the first year treatment^[20]. Patients must be informed of these relevant results, which should be taken into account in the treatment selection process.

There is also some controversy surrounding the treatment indication in patients with significant comorbidities given that their systematic exclusion from most phase III trials. As a result, treatment selection in these cases largely depends on studies with lower levels of evidence and on the treating specialist’s experience with these drugs in

Table 1 Characteristics of the randomized phase 3 trials of second-generation antihormonal treatments in metastatic hormone-sensitive prostate cancer

Trial	Treatment	n	Inclusion criteria	Stratification	Main objective	Secondary objectives
LATITUDE (Fizazi K <i>et al</i> ^[16]) 2017	ABIRATERONE 1000 mg + PREDNISON 5 mg + ADT; PLACEBO + ADT	597; 602	High risk con ≥ 2 factors: (1) Gleason 8-10; (2) ≥ 3 bone METS; (3) Evaluable visceral METS; and (4) ECOG PS ≤ 2	Visceral METS (yes/no); ECOG PS (0, 1/2)	OSrPFS	Time to pain progression; Time to PSA progression; Development of skeletal events; Time to chemotherapy; Time to new treatment; QoL
STAMPEDE (James <i>et al</i> ^[17]) ¹ 2017	ABIRATERONE 1000 mg + PREDNISON 5 mg + ADT; ADT	502; 500	Presence of METS	ECOG PS (0/1, 2); AGE ($< 70/\geq 70$); Use of steroids (yes/no); Research centre; Indication for RT (yes/no); Type of ADT	OS	PFS; Failure-free survival; Cancer-specific survival; Time to skeletal events; Toxicity; QoL
ENZAMET (Davis <i>et al</i> ^[13]) 2019	ENZALUTAMIDE 160 mg + ADT; ANTIANDROGENS (bicalutamide, flutamide or nilutamide) + ADT	563; 562	Low and high volume defined: (1) Visceral METS; and (2) ≥ 4 bone METS, at least 1 outside vertebral column or pelvis. ECOG PS ≤ 2	Volume (high/low); Docetaxel (yes/no); Comorbidities (0-1/2-3); Antiresorptive treatment (yes/no); Research centre	OS	PFS; PSA response; Adverse effects; QoL; Cost-effectiveness
TITAN (Chi <i>et al</i> ^[15]) 2019	Apalutamide 240 mg + ADT; PLACEBO + ADT	525; 527	LOW AND HIGH VOLUME DEFINED: (1) Visceral METS + ≥ 1 bone METS; and (2) ≥ 4 bone METS, at least 1 outside vertebral column or pelvis. ECOG PS 0-1; ≥ 1 bone METS on bone scan	Gleason ($\leq 7/\geq 8$); Docetaxel (yes/no); Geographic region	OS; rPFS	Time to pain progression; Time to opioids; Time to skeletal events; Time to chemotherapy; Time to PSA progression; Survival to 2 nd progression; Time to symptomatic local progression; QoL
ARCHES (Armstrong <i>et al</i> ^[14]) 2019	ENZALUTAMIDE 160 mg + ADT; PLACEBO + ADT	574; 576	ECOG PS 0-1; low and high volume defined: (1) Visceral METS; and (2) ≥ 4 bone METS, at least 1 outside vertebral column or pelvis	Volume (high/low); Docetaxel (no/0-5 cycles/ ≥ 6)	rPFS; Evaluated at 24 wk	Time to PSA progression; Time to skeletal events; Time to new treatment; Undetectable PSA; Objective response rate; OS; Time to worsening of urinary symptoms; Time to pain progression; Time to castration-resistance; Time to QoL worsening; PROS

¹Only patients with metastases. ADT: Androgen deprivation therapy; METS: Metastases; OS: Overall survival; PROs: Patient-reported outcomes; PS: Performance status; PSA: Prostate-specific antigen; QoL: Quality of life; rPFS: Radiographic progression-free survival; RT: Radiotherapy.

other clinical settings for which they are approved. In any case, an individualized assessment of each patient should be performed to determine the most appropriate treatment, which should also take into account differences in the side-effect profiles of second-generation antihormonal therapies. Similarly, cost-effectiveness and the optimal sequencing of these drugs with docetaxel are also key factors to consider^[21,22]. Unfortunately, the optimal sequence is not known due to the lack of data from randomized clinical trials. The mechanism of action of docetaxel differs from that of second-generation antiandrogens. Therefore, administration of docetaxel in patients with progressive disease after treatment with these second-generation antiandrogens would conceivably eliminate treatment-resistant cell clones (regardless of the specific androgen receptor pathway), thereby permitting the use of another ARSi in patients who develop progression.

Treatment of the primary tumour with surgery or radiotherapy plays an important role in treatment outcomes. The role of radiotherapy to the primary was evaluated in both the HORRAD^[23] and STAMPEDE trials (arm H)^[24], adding another dimension to the discussion about the indication for radiotherapy in metastatic disease. The available evidence for surgical treatment of the primary tumour in this clinical setting is contradictory, and the evidence to support its use is weak^[25,26]. However, the role of surgery is currently being evaluated in large trials, which will help to determine the value of this approach in this clinical setting. By contrast, the results of the STAMPEDE trial (arm H) confirmed a statistically significant benefit for radiotherapy to the primary in terms of improved 3-yr OS (increase of 8%) in patients with low-volume disease (CHAARTED criteria). Even though the study design did not stratify patients into low- and high-volume disease, an in-depth analysis of the trial results confirmed the validity of stratification according to metastatic burden, leading the

Table 2 Survival and toxicity results of the phase 3 randomized clinical trials of second-generation antihormonal treatments in metastatic hormone-sensitive prostate cancer

Trial	Follow-up in mo	Main results	Quality of life	Toxicity
LATITUDE	51.8	Reduced mortality risk by 34% with abiraterone ($P < 0.001$); OS at 3 yr (66% vs 49%); median OS (53.3 mo vs 36.5 mo). Reduction in risk of radiographic progression by 53% with abiraterone ($P < 0.001$) (33 mo vs 14.8 mo)	Abiraterone improved all QoL-related parameters	Toxicity grade 3-4: (1) Abiraterone: 63%; (2) Placebo: 48%. Treatment-related deaths: (1) Abiraterone: 5%; and (2) Placebo: 4%
STAMPEDE	40	Reduction in mortality risk of 39% with abiraterone ($P < 0.001$). Reduction in risk of progression of 69% with abiraterone ($P < 0.001$). Treatment benefit in all patients according to risk group and disease volume	-	Toxicity grade ≥ 3 : (1) Abiraterone: 47%; and (2) ADT: 33%
ENZAMET	33	Reduction in mortality risk by 67% with enzalutamide ($P = 0.002$). 3-yr OS (82% vs 72%)	No SD	Toxicity grade ≥ 3 : (1) Enzalutamide: 58%; and (2) AA: 43%
TITAN	22.7	Reduction in risk of radiographic progression or death by 52% with apalutamide ($P < 0.001$). 2-yr rPFS (68.2% vs 47.5%). Reduction in mortality risk of 33% with apalutamide ($P = 0.005$). 2-yr OS (82.4% vs 73.5%). Treatment benefit in all patients according to disease volume, significant in rPFS and OS in high-volume disease	No SD	Toxicity grade 3-4: (1) Apalutamide: 42.2%; and (2) Placebo: 40.8%. Treatment-related deaths: (1) Apalutamide: 1.9%; and (2) Placebo: 3%
ARCHES	14.4	Reduction in risk of radiographic progression or death of 61% with enzalutamide ($P < 0.001$) (NR vs 19 mo). OS ($P = 0.336$). Benefit in rPFS in both high and low volume disease	No SD	No SD. Treatment-related deaths: (1) Enzalutamide: 2.4%; and (2) Placebo: 1.7%

AA: First-generation antiandrogens; ADT: Androgen deprivation therapy; NR: Not reached; OS: Overall survival; QoL: Quality of life; rPFS: Radiographic progression-free survival; SD: Statistical differences.

authors to conclude that radiotherapy to the primary should be considered the new standard of care in low-volume mHSPC given that it does not worsen local symptomatic events^[27]. However, there is some uncertainty regarding the magnitude of benefit of radiotherapy in patients who receive systemic treatment with docetaxel, abiraterone acetate, enzalutamide, or apalutamide given that only 18% of patients in the H arm of the STAMPEDE trial received chemotherapy, and none received second-generation antihormonal therapy. In this regard, the results of the PEACE-1 trial (NCT01957436) are expected to resolve this question when they are published.

Another important unresolved question—despite a growing body of favourable data—is the role of stereotactic body radiotherapy to the bone and/or lymph node metastases in oligometastatic patients. Conceivably, stereotactic body radiotherapy should complement the positive effects of radiotherapy to the primary combined with systemic therapy, although the magnitude of the benefit of administering all three treatments remains unknown.

CONCLUSION

Androgen receptor inhibitors, whose clinical utility was first demonstrated in advanced PCa, now are part of the therapeutic arsenal for mHSPC. Given the demonstrated superiority ARSi plus ADT vs ADT alone, the indication for ADT monotherapy is now limited to patients with significant comorbidity and a short life expectancy, or to patients who refuse combination therapy, despite the clear benefits.

Chemotherapy has shown a clear benefit as initial treatment in patients with high-volume disease. However, selection of the “optimal” treatment must take into account the toxicity profile of the treatment as well as its impact on QoL, especially given the wide array of alternative treatments—including abiraterone acetate, enzalutamide, and apalutamide—all of which have shown excellent clinical results with substantially less toxicity than chemotherapy and thus less of a negative impact on QoL.

Currently, radiotherapy to the primary tumour is considered the new standard of care in patients with low-volume disease, at least until results are published to clarify the impact of treatment intensification, including both the treatment of metastatic lesions and the combination of local treatments with novel systemic therapies.

REFERENCES

- 1 **Goldenberg SL**, Bruchofsky N. Hormonal manipulation for metastatic prostate cancer. Androgen withdrawal therapy: new perspectives in the treatment of prostate cancer. In: Principles and practices of genitourinary. Derek Raghavan, Howard I Scheer, Steven A Leibel and Paul H Lange. Lippincott-Raven Publishers, Philadelphia; 1997: 583-591
- 2 **Shore ND**, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, Akaza H, Bossi A, van Veenhuyzen DF, Selby B, Fan X, Kang V, Walling J, Tombal B; HERO Study Investigators. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. *N Engl J Med* 2020; **382**: 2187-2196 [PMID: [32469183](#) DOI: [10.1056/NEJMoa2004325](#)]
- 3 **Schmid HP**, Bitton A. [Therapeutic options in advanced cancer of the prostate]. *Praxis (Bern 1994)* 1997; **86**: 1734-1739 [PMID: [9446174](#)]
- 4 **Bubley GJ**, Balk SP. Treatment of Androgen-Independent Prostate Cancer. *Oncologist* 1996; **1**: 30-35 [PMID: [10387966](#) DOI: [10.1634/theoncologist.1-1-30](#)]
- 5 **Ng K**, Smith S, Shamash J. Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Advances and Treatment Strategies in the First-Line Setting. *Oncol Ther* 2020; **8**: 209-230 [PMID: [32700045](#) DOI: [10.1007/s40487-020-00119-z](#)]
- 6 **Kinsey EN**, Zhang T, Armstrong AJ. Metastatic Hormone-Sensitive Prostate Cancer: A Review of the Current Treatment Landscape. *Cancer J* 2020; **26**: 64-75 [PMID: [31977388](#) DOI: [10.1097/PPO.0000000000000418](#)]
- 7 **Hussain M**, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G, Wilding G, Prescott S, Kanaga Sundaram S, Small EJ, Dawson NA, Donnelly BJ, Venner PM, Vaishampayan UN, Schellhammer PF, Quinn DI, Raghavan D, Ely B, Moinpour CM, Vogelzang NJ, Thompson IM Jr. Intermittent vs continuous androgen deprivation in prostate cancer. *N Engl J Med* 2013; **368**: 1314-1325 [PMID: [23550669](#) DOI: [10.1056/NEJMoa1212299](#)]
- 8 **Sweeney CJ**, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med* 2015; **373**: 737-746 [PMID: [26244877](#) DOI: [10.1056/NEJMoa1503747](#)]
- 9 **James ND**, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G, de Bono J, Cross W, Jones RJ, Thalmann G, Amos C, Matheson D, Millman R, Alzouebi M, Beesley S, Birtle AJ, Brock S, Cathomas R, Chakraborti P, Chowdhury S, Cook A, Elliott T, Gale J, Gibbs S, Graham JD, Hetherington J, Hughes R, Laing R, McKinna F, McLaren DB, O'Sullivan JM, Parikh O, Peedell C, Protheroe A, Robinson AJ, Srihari N, Srinivasan R, Staffurth J, Sundar S, Tolan S, Tsang D, Wagstaff J, Parmar MK; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016; **387**: 1163-1177 [PMID: [26719232](#) DOI: [10.1016/S0140-6736\(15\)01037-5](#)]
- 10 **Mottet N**, Cornford P, van den Bergh RCN, Briers E, De Santis M, Fanti S, et al EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2019. In: European Association of Urology Guidelines 2019. EAU Guidelines Office, Arnhem, The Netherlands; 2019: 1-161
- 11 **Gravis G**, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM, Pouessel D, Mourey L, Beuzeboc P, Zanetta S, Habibian M, Berdah JF, Dauba J, Baciuchka M, Platini C, Linassier C, Labourey JL, Machiels JP, El Kouri C, Ravaud A, Suc E, Eymard JC, Hasbini A, Bousquet G, Soulie M. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013; **14**: 149-158 [PMID: [23306100](#) DOI: [10.1016/S1470-2045\(12\)70560-0](#)]
- 12 **Clarke NW**, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, Brawley CD, Calvert J, Chowdhury S, Cook A, Cross W, Dearnaley DP, Douis H, Gilbert D, Gillessen S, Jones RJ, Langley RE, MacNair A, Malik Z, Mason MD, Matheson D, Millman R, Parker CC, Ritchie AWS, Rush H, Russell JM, Brown J, Beesley S, Birtle A, Capaldi L, Gale J, Gibbs S, Lydon A, Nikapota A, Omlin A, O'Sullivan JM, Parikh O, Protheroe A, Rudman S, Srihari NN, Simms M, Tanguay JS, Tolan S, Wagstaff J, Wallace J, Wylie J, Zarkar A, Sydes MR, Parmar MKB, James ND. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol* 2019; **30**: 1992-2003 [PMID: [31560068](#) DOI: [10.1093/annonc/mdz396](#)]
- 13 **Davis ID**, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ; ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med* 2019; **381**: 121-131 [PMID: [31157964](#) DOI: [10.1056/NEJMoa1903835](#)]
- 14 **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. 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* 2019; **37**: 2974-2986 [PMID: [31157964](#) DOI: [10.1200/JCO.2018.37.2974](#)]

- 31329516 DOI: [10.1200/JCO.19.00799](https://doi.org/10.1200/JCO.19.00799)]
- 15 **Chi KN**, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, DePrince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S; TITAN Investigators. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2019; **381**: 13-24 [PMID: [31150574](https://pubmed.ncbi.nlm.nih.gov/31150574/) DOI: [10.1056/NEJMoa1903307](https://doi.org/10.1056/NEJMoa1903307)]
 - 16 **Fizazi K**, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyereabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN; LATITUDE Investigators. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017; **377**: 352-360 [PMID: [28578607](https://pubmed.ncbi.nlm.nih.gov/28578607/) DOI: [10.1056/NEJMoa1704174](https://doi.org/10.1056/NEJMoa1704174)]
 - 17 **James ND**, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, Attard G, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR; STAMPEDE Investigators. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med* 2017; **377**: 338-351 [PMID: [28578639](https://pubmed.ncbi.nlm.nih.gov/28578639/) DOI: [10.1056/NEJMoa1702900](https://doi.org/10.1056/NEJMoa1702900)]
 - 18 **Fizazi K**, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyereabend S, Protheroe A, Sulur G, Luna Y, Li S, Mundle S, Chi KN. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2019; **20**: 686-700 [PMID: [30987939](https://pubmed.ncbi.nlm.nih.gov/30987939/) DOI: [10.1016/S1470-2045\(19\)30082-8](https://doi.org/10.1016/S1470-2045(19)30082-8)]
 - 19 **Hoyle AP**, Ali A, James ND, Cook A, Parker CC, de Bono JS, Attard G, Chowdhury S, Cross WR, Dearnaley DP, Brawley CD, Gilson C, Ingleby F, Gillessen S, Aebbersold DM, Jones RJ, Matheson D, Millman R, Mason MD, Ritchie AWS, Russell M, Douis H, Parmar MKB, Sydes MR, Clarke NW; STAMPEDE Investigators. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. *Eur Urol* 2019; **76**: 719-728 [PMID: [31447077](https://pubmed.ncbi.nlm.nih.gov/31447077/) DOI: [10.1016/j.eururo.2019.08.006](https://doi.org/10.1016/j.eururo.2019.08.006)]
 - 20 **Rush HL**, Cook AD, Brawley CD, Murphy L, Macnair A, Millman R, Attard G, Clarke N, Morgans AK, Chowdhury S, Gilbert DC, Dearnaley DP, Sydes MR, James ND, Langley RE, Parmar MKB, STAMPEDE Investigators. Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial. *J Clin Oncol* 2020; **38**: 14 [DOI: [10.1200/JCO.2020.38.6_suppl.14](https://doi.org/10.1200/JCO.2020.38.6_suppl.14)]
 - 21 **Wallis CJD**, Klaassen Z, Bhindi B, Goldberg H, Chandrasekar T, Farrell AM, Boorjian SA, Kulkarni GS, Karnes RJ, Satkunasivam R. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naïve Prostate Cancer: A Systematic Review and Network Meta-analysis. *Eur Urol* 2018; **73**: 834-844 [PMID: [29037513](https://pubmed.ncbi.nlm.nih.gov/29037513/) DOI: [10.1016/j.eururo.2017.10.002](https://doi.org/10.1016/j.eururo.2017.10.002)]
 - 22 **Catrin C**, Castro E, Lozano R, Zanardi E, Rubagotti A, Boccardo F, Olmos D. Current Treatment Options for Metastatic Hormone-Sensitive Prostate Cancer. *Cancers (Basel)* 2019; **11** [PMID: [31547436](https://pubmed.ncbi.nlm.nih.gov/31547436/) DOI: [10.3390/cancers11091355](https://doi.org/10.3390/cancers11091355)]
 - 23 **Boevé LMS**, Hulshof MCCM, Vis AN, Zwinderman AH, Twisk JWR, Witjes WPJ, Delaere KPJ, Moorselaar RJA, Verhagen PCMS, van Andel G. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. *Eur Urol* 2019; **75**: 410-418 [PMID: [30266309](https://pubmed.ncbi.nlm.nih.gov/30266309/) DOI: [10.1016/j.eururo.2018.09.008](https://doi.org/10.1016/j.eururo.2018.09.008)]
 - 24 **Parker CC**, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, Ritchie AWS, Attard G, Chowdhury S, Cross W, Dearnaley DP, Gillessen S, Gilson C, Jones RJ, Langley RE, Malik ZI, Mason MD, Matheson D, Millman R, Russell JM, Thalmann GN, Amos CL, Alonzi R, Bahl A, Birtle A, Din O, Douis H, Eswar C, Gale J, Gannon MR, Jonnada S, Khaksar S, Lester JF, O'Sullivan JM, Parikh OA, Pedley ID, Pudney DM, Sheehan DJ, Srihari NN, Tran ATH, Parmar MKB, Sydes MR; Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018; **392**: 2353-2366 [PMID: [30355464](https://pubmed.ncbi.nlm.nih.gov/30355464/) DOI: [10.1016/S0140-6736\(18\)32486-3](https://doi.org/10.1016/S0140-6736(18)32486-3)]
 - 25 **Fossati N**, Trinh QD, Sammon J, Sood A, Larcher A, Sun M, Karakiewicz P, Guazzoni G, Montorsi F, Briganti A, Menon M, Abdollah F. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. *Eur Urol* 2015; **67**: 3-6 [PMID: [25217422](https://pubmed.ncbi.nlm.nih.gov/25217422/) DOI: [10.1016/j.eururo.2014.08.056](https://doi.org/10.1016/j.eururo.2014.08.056)]
 - 26 **Tilki D**, Pompe RS, Bandini M, Marchioni M, Kretschmer A, Tian Z, Karakiewicz PI, Evans CP. Local treatment for metastatic prostate cancer: A systematic review. *Int J Urol* 2018; **25**: 390-403 [PMID: [29572963](https://pubmed.ncbi.nlm.nih.gov/29572963/) DOI: [10.1111/iju.13535](https://doi.org/10.1111/iju.13535)]
 - 27 **Burdett S**, Boevé LM, Ingleby FC, Fisher DJ, Rydzewska LH, Vale CL, van Andel G, Clarke NW, Hulshof MC, James ND, Parker CC, Parmar MK, Sweeney CJ, Sydes MR, Tombal B, Verhagen PC, Tierney JF; STOPCAP M1 Radiotherapy Collaborators. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. *Eur Urol* 2019; **76**: 115-124 [PMID: [30826218](https://pubmed.ncbi.nlm.nih.gov/30826218/) DOI: [10.1016/j.eururo.2019.02.003](https://doi.org/10.1016/j.eururo.2019.02.003)]



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