doi.org/10.58931/cot.2026.3145

## About the Authors


### Ahmad Gebai, MD, MSc

Dr. Ahmad Gebai is a Medical Oncology resident at the Université de Montréal. He completed his medical degree and residency training in Internal Medicine at the Université de Montréal as well and holds a master's degree in Biochemistry from McGill University. His training reflects a strong foundation in both clinical medicine and translational science.

***Affiliations:*** Université de Montréal, Montréal, QC



### Zineb Hamilou, MD

Dr. Zineb Hamilou is a hematologist and medical oncologist trained at the University of Montreal. She is an assistant professor at the University of Montreal and an investigator at the CHUM Research Centre. She completed postdoctoral training in genitourinary cancers with a particular interest in prostate cancer. Within the oncology and uro-oncology research team, she participates in the care of patients enrolled in multiple phase I, II, III research protocols.

***Affiliations:*** Department of Medicine, Hematology-Oncology Division, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC


# Metastatic CRPC: Contemporary Therapeutic Options and Optimal Sequencing


**Ahmad Gebai, MD, MSc**
**Zineb Hamilou, MD**


## Introduction

Prostate cancer (PC) is the most common malignancy among men worldwide. In Canada, an estimated 27,900 new diagnoses were projected in 2024, accounting for approximately 22% of all new cancer cases, with nearly 5,000 related deaths, making PC the fifth leading cause of cancer mortality.[1] Approximately 8% of patients present with metastatic disease at diagnosis.[2] Moreover, rates of *de novo* metastatic PC have increased in recent years, likely reflecting both the widespread adoption of advanced imaging modalities and reduced systematic screening practices.[2,3]

Initial treatment for recurrent or *de novo* metastatic castration-sensitive prostate cancer (mCSPC) typically consists of androgen-deprivation therapy (ADT) combined with an androgen receptor pathway inhibitor (ARPI). In patients with high-volume disease, which is

defined as ≥4 bone metastases (including ≥1 outside the vertebral column) or the presence of visceral metastases, triplet therapy with ADT, an ARPI, and docetaxel chemotherapy may be employed.[4-6] In contrast, biochemical recurrence without radiographic metastases is generally managed with ADT alone, with treatment intensification using enzalutamide for patients with a prostate-specific antigen (PSA) doubling time between 3 and 9 months, as supported by the EMBARK trial.[7]

Despite initial disease control, most patients ultimately progress while maintaining castrate testosterone levels, a state known as castration-resistant prostate cancer (CRPC), which may be metastatic (mCRPC) or non-metastatic (nmCRPC). Over 84% of patients are estimated to have metastatic disease at the time of CRPC diagnosis.[8]

This review summarizes the current and evolving treatment landscape for mCRPC and proposes an evidence-based approach to treatment sequencing in accordance with the 2025 Canadian Urological Association Canadian Uro-Oncology Group guidelines and the National Comprehensive Cancer Network (NCCN) recommendations.[9,10]

## General Principles for Treatment Selection

Metastatic CRPC is defined by disease progression despite ongoing ADT and castrate serum testosterone levels (<50 ng/dL or <1.7 nmol/L). Persistent androgen receptor signaling remains a key driver of disease progression, partly due to intratumoural autocrine and paracrine androgen synthesis.[11] Consequently, ADT is maintained indefinitely in patients with mCRPC.

Biochemical progression is defined as a PSA rise of ≥2 ng/mL or ≥50% above nadir, confirmed by three consecutive measurements at least one week apart.[12] Radiographic progression is assessed according to Prostate Cancer Working Group 3 (PCWG3) criteria.[13]

For patients who developed mCRPC, biopsy of metastatic lesions is recommended when feasible, along with molecular testing for homologous recombination repair (HRR) gene mutations (particularly *BRCA*1/2) and microsatellite instability (MSI)/mismatch repair (MMR) deficiency.[9,10] HRR testing may be performed on archival primary tumour tissue, fresh metastatic biopsy, or circulating tumour DNA when tissue is unavailable or non-informative.

Given the increasing use of ARPIs and chemotherapy in earlier disease states, treatment sequencing in mCRPC has become increasingly complex and must account for prior therapies, response duration, toxicity, and patient comorbidities.

## Androgen Receptor Pathway Inhibitors

Abiraterone acetate plus prednisone (AAP) was the first ARPI to demonstrate survival benefit in mCRPC. In a phase III trial involving post-chemotherapy patients, AAP significantly improved progression-free survival (PFS) and overall survival (OS) compared with placebo.[14] Subsequently, the COU-AA-302 trial showed that AAP significantly prolonged median PFS in patients with chemotherapy-naïve mCRPC (16.5 vs. 8.3 months; hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.45–0.62), leading to its approval in this setting.[15]

Enzalutamide, a second-generation ARPI, also demonstrated OS and PFS benefits in mCRPC after chemotherapy in the AFFIRM trial.[16] In the PREVAIL trial, enzalutamide significantly improved OS in patients with chemotherapy-naïve mCRPC, with a median OS of 35.2 versus 31.0 months (HR: 0.71, 95% CI: 0.60–0.84).[17,18]

In nmCRPC, enzalutamide, apalutamide, and darolutamide have all demonstrated clinically meaningful improvements in metastasis-free survival and OS when added to continuous ADT in patients with high-risk disease (PSA doubling time ≤10 months), forming the standard of care in this setting.[19-21]

For patients presenting with *de novo* mCRPC who have previously received ADT alone, first-line treatment typically consists of an ARPI (AAP or enzalutamide), either alone or in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor in the presence of HRR mutations.

## Taxane Chemotherapy

Taxane chemotherapy remains a cornerstone of mCRPC treatment. Docetaxel demonstrated a median OS improvement of approximately 3 months over mitoxantrone in the TAX 327 trial and is most commonly used as first-line chemotherapy.[22]

Cabazitaxel, a next-generation taxane developed to overcome docetaxel resistance, has

demonstrated efficacy across multiple trials. In the TROPIC trial, cabazitaxel improved OS compared with mitoxantrone in post-docetaxel patients (15.1 vs. 12.7 months; HR: 0.70, 95% CI: 0.59–0.83).[23] The PROSELICA trial established non-inferiority of the 20 mg/m² dose compared with 25 mg/m², with improved tolerability.[24] Importantly, the CARD trial showed that cabazitaxel was superior to switching to an alternative ARPI in patients previously treated with docetaxel and one ARPI, improving both radiographic PFS (8.0 vs. 3.7 months; HR: 0.54, 95% CI: 0.40–0.73) and OS (13.6 vs.11.0 months; HR: 0.64, 95% CI: 0.46–0.89).[25]

## Targeted Therapies

### HRR Gene Mutations and PARP Inhibitors

Up to 30% of patients with metastatic PC harbour germline or somatic DNA repair gene alterations, most commonly involving *BRCA2* or *BRCA1*.[26-29] These mutations are associated with poorer prognosis but confer sensitivity to PARP inhibition.

In the post-ARPI setting, the PROfound trial demonstrated that olaparib significantly improved radiographic PFS (7.4 vs. 3.6 months; HR: 0.34, 95% CI: 0.25–0.47) and OS (18.5 vs. 15.1 months; HR: 0.69, 95% CI: 0.50–0.97) compared with switching to another ARPI in patients with *BRCA1/2* or *ATM* alterations, despite crossover.[30]

First-line combinations of PARP inhibitors with ARPIs have also shown benefit in first-line treatment of mCRPC. The PROpel trial demonstrated improved radiographic PFS with olaparib plus abiraterone compared with abiraterone alone (24.8 vs. 16.6 months; HR: 0.66; 95% CI: 0.54 to 0.81), with the greatest benefit observed in HRR-mutated tumours.[31] This combination is approved by Health Canada for *BRCA1/2*-mutated mCRPC.

Similarly, the MAGNITUDE trial showed improved PFS with niraparib plus AAP in HRR-mutated mCRPC.[32] Recently, the TALAPRO-2 trial demonstrated that talazoparib plus enzalutamide improved both PFS and OS compared with enzalutamide alone, irrespective of HRR status. This treatment resulted in radiographic mPFS of 33.1 vs. 19.5 months (HR: 0.667, 95% CI: 0.551–0.807) and an OS of 45.8 vs. 37.0 months (HR: 0.796, 95% CI: 0.661–0.958).[33] The benefit was most pronounced in HRR-mutated tumours, where the combination produced a deeper and more durable radiographic PFS advantage compared with HRR-non-mutated disease.

### PSMA-Targeted Radioligand Therapy

Patients with mCRPC progressing after ARPI and taxane chemotherapy may be eligible for PSMA-targeted radioligand therapy (RLT), contingent upon PSMA positron emission tomography (PET) imaging demonstrating PSMA-positive disease without discordant PSMA-negative lesions.

In the phase III VISION trial, beta-emitter lutetium-177-PSMA-617 plus standard of care significantly improved radiographic PFS (8.7 vs. 3.4 months; HR: 0.40, 99.2% CI: 0.29–0.57) and OS (15.3 vs. 11.3 months; HR: 0.62, 95% CI: 0.52–0.74) compared with standard care alone.[34] Although higher rates of grade ≥3 adverse events were observed, quality of life was preserved.

In taxane-naïve mCRPC, the PSMAfore and SPLASH trials demonstrated significant improvements in radiographic PFS compared with ARPI switching, though no OS benefit was observed, likely due to crossover.[35,36]

### Immunotherapy

MMR deficiency, MSI-high status, or high tumour mutational burden (TMB) are identified in a minority of patients with mCRPC (1.2–12.0%) and may predict benefit from immune checkpoint inhibition.[28] Pembrolizumab has tumour-agnostic approval for these patients, with retrospective data demonstrating meaningful PSA and radiographic responses.[28,37] However, phase III trials of pembrolizumab combinations in unselected mCRPC populations have not demonstrated survival benefit.[38-40]

### Other Therapies

Alpha-emitter Radium-223 dichloride ($^{223}$Ra) demonstrated improved OS and delayed skeletal-related events in the ALSYMPCA trial for patients with symptomatic bone-only mCRPC.[41] $^{223}$Ra is an option for patients with mCRPC with symptomatic bone metastases and/or lymph nodes ≤3 cm in the absence of visceral disease.

Mitoxantrone, an anthracenedione antineoplastic agent, provides palliative benefit without OS improvement and is now rarely used.[42,43] The cellular therapy sipuleucel-T improved OS in asymptomatic mCRPC in the IMPACT trial but is not approved by Health Canada.[44]

## Supportive Therapy

Bone metastases occur in approximately 90% of patients with mCRPC and these patients are thus subject to skeletal-related events.[45-47] These include pathological fractures, debilitating bone pain requiring palliative radiation therapy, and spinal cord compression, all of which may significantly affect quality of life.

Zoledronic acid and denosumab reduce skeletal-related events, with denosumab demonstrating superiority over zoledronic acid in delaying time to first event.[46,47] Bone-modifying agents should be routinely considered, with appropriate dental evaluation to mitigate the risk of osteonecrosis of the jaw.

## Treatment Sequencing

Treatment sequencing in mCRPC is largely driven by prior systemic therapy exposure and should be individualized based on clinical and biological characteristics, as well as patient comorbidities.

Approximately 20–50% of patients treated with curative intent ultimately develop biochemical recurrence and progress to mCRPC, most often after prior exposure to ADT and an ARPI. Upon development of castration resistance, these patients typically transition to docetaxel chemotherapy while continuing ADT.

Similarly, patients presenting with (mCSPC) are now frequently treated upfront with ADT in combination with an ARPI, with the addition of docetaxel in those with high-volume disease. At progression to mCRPC, docetaxel is initiated, if not previously administered, or may be reintroduced in selected patients who achieved a durable prior response.

In contrast, for patients harbouring a pathogenic *BRCA1* or *BRCA2* mutation who experience progression following ARPI therapy, treatment with a PARP inhibitor, most notably olaparib, is recommended in lieu of immediate taxane chemotherapy.

As discussed earlier, lutetium-177-PSMA-617 may be considered in patients with prior exposure to an ARPI and at least one line of chemotherapy.

Finally, cabazitaxel and $^{223}$Ra represent established therapeutic options that can be incorporated into the treatment sequence based on disease characteristics, prior therapies, symptom burden, and patient fitness.

## Conclusion

Therapeutic advances have substantially improved outcomes for patients with mCRPC, offering prolonged survival and improved quality of life. Nonetheless, the disease remains incurable, and optimal sequencing of increasingly complex treatment options requires careful consideration of prior therapies and molecular features. Participation in clinical trials remains essential to further advance care for this population.

## Correspondence

**Zineb Hamilou, MD**
**Email:** zineb.hamilou.med@ssss.gouv.qc.ca

## Financial Disclosures

**A.G.:** None declared.
**Z.H.: Honorarium for consultations and conferences:** AstraZeneca, EMD Serono/Pfizer, Astellas, Merck, Novartis; **Honorarium for conferences:** Canadian Urology Association, Association des médecins hématologues et oncologues du Québec, Fédération des médecins spécialistes du Québec; **Research Grant:** AstraZeneca

## References

1. Brenner DR, Gillis J, Demers AA, Ellison LF, Billette JM, Zhang SX, et al. Projected estimates of cancer in Canada in 2024. CMAJ. 2024;196(18):E615-23. https://doi.org/10.1503/cmaj.240095
2. Canadian Cancer Society. Cancer statistics [Internet]. Toronto (ON): Canadian Cancer Society; [cited 2026 Jan 7]. Available from: https://cancer.ca/en/research/cancer-statistics
3. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. CA Cancer J Clin. 2025;75(1):10-45. https://doi.org/10.3322/caac.21871
4. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373(8):737-46. https://doi.org/10.1056/nejmoa1503747
5. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med. 2022;386(12):1132-42. https://doi.org/10.1056/nejmoa2119115
6. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Flechon A, et al. 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.

2022;399(10336):1695-707. https://doi.org/10.1016/S0140-6736(22)00367-1
7. Freedland SJ, de Almeida Luz M, De Giorgi U, Gleave M, Gotto GT, Pieczonka CM, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med. 2023;389(16):1453-65. https://doi.org/10.1056/NEJMoa2303974
8. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011;65(11):1180-92. https://doi.org/10.1111/J.1742-1241.2011.02799.X
9. Saad F, So AI, Aprikian A, Finelli A, Fleshner NE, Gleave ME, et al. 2025 Canadian Urological Association-Canadian Uro-oncology Group Guideline: Metastatic castration-resistant prostate cancer (Update). Can Urol Assoc J. 2025;19(8):E276-E89. https://doi.org/10.5489/cuaj.9341
10. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed December 12th 2025.
11. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. Endocr Relat Cancer. 2011;18(5):R175-82. https://doi.org/10.1530/ERC-10-0339
12. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630-42. https://doi.org/10.1016/j.eururo.2016.08.002
13. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18. https://doi.org/10.1200/JCO.2015.64.2702
14. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005. https://doi.org/10.1056/NEJMoa1014618
15. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-48. https://doi.org/10.1056/NEJMoa1209096
16. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97. https://doi.org/0.1056/NEJMoa1207506
17. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33. https://doi.org/10.1056/NEJMoa1405095
18. Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua AM, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol. 2020;78(3):347-57. https://doi.org/10.1016/j.eururo.2020.04.061
19. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2020;382(23):2197-206. https://doi.org/10.1056/NEJMoa2003892
20. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-18. https://doi.org/10.1056/NEJMoa1715546
21. Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019;380(13):1235-46. https://doi.org/10.1056/NEJMoa1815671
22. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12. https://doi.org/10.1056/NEJMOA040720
23. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54. https://doi.org/10.1016/S0140-6736(10)61389-X
24. Eisenberger M, Hardy-Bessard AC, Kim CS, Geczi L, Ford D, Mourey L, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol. 2017;35(28):3198-206. https://doi.org/10.1200/JCO.2016.72.1076
25. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019;381(26):2506-18. https://doi.org/10.1056/NEJMoa1911206
26. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375(5):443-53. https://doi.org/10.1056/NEJMoa1603144
27. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161(5):1215-28. https://doi.org/10.1016/j.cell.2015.05.001
28. Abida W, Armenia J, Gopalan A, Brennan R, Walsh M, Barron D, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol. 2017;2017. https://doi.org/10.1200/PO.17.00029
29. Abida W, Cheng ML, Armenia J, Middha S, Autio KA, Vargas HA, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019;5(4):471-8. https://doi.org/10.1001/JAMAONCOL.2018.5801
30. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu

S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091-102. https://doi.org/10.1056/NEJMoa1911440
31. Saad F, Clarke NW, Oya M, Shore N, Procopio G, Guedes JD, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24(10):1094-108. https://doi.org/10.1016/S1470-2045(23)00382-0
32. Chi KN, Sandhu S, Smith MR, Attard G, Saad M, Olmos D, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol. 2023;34(9):772-82. https://doi.org/10.1016/j.annonc.2023.06.009
33. Agarwal N, Azad AA, Carles J, Fay AP, Matsubara N, Heinrich D, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402(10398):291-303. https://doi.org/10.1016/S0140-6736(23)01055-3
34. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med. 2021;385(12):1091-103. https://doi.org/10.1056/NEJMOA2107322
35. Morris MJ, Castellano D, Herrmann K, de Bono JS, Shore ND, Chi KN, et al. (177)Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet. 2024;404(10459):1227-39. https://doi.org/10.1016/S0140-6736(24)01653-2
36. Sartor O, Jiang DM, Smoragiewicz M, Zibelman M, Flechon A, El-Haddad G, et al. Efficacy of $^{177}$Lu-PNT2002 in PSMA-positive mCRPC following progression on an androgen-receptor pathway inhibitor (SPLASH). Presented at: European Society for Medical Oncology (ESMO) Congress 2024; 13-17 September 2024; Barcelona, Spain. Abstract LBA65.
37. Graham LS, Montgomery B, Cheng HH, Yu EY, Nelson PS, Pritchard C, et al. Mismatch repair deficiency in metastatic prostate cancer: Response to PD-1 blockade and standard therapies. PLoS One. 2020;15(5):e0233260. https://doi.org/10.1371/JOURNAL.PONE.0233260
38. Graff JN, Burotto M, Fong PC, Pook DW, Zurawski B, Manneh Kopp R, et al. Pembrolizumab plus enzalutamide versus placebo plus enzalutamide for chemotherapy-naive metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-641 study. Ann Oncol. 2025;36(8):976-87. https://doi.org/10.1016/j.annonc.2025.05.007
39. Petrylak DP, Ratta R, Matsubara N, Korbenfeld E, Gafanov R, Mourey L, et al. Pembrolizumab plus docetaxel versus docetaxel for previously treated metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-921 trial. J Clin Oncol. 2025;43(14):1638-49. https://doi.org/10.1200/JCO-24-01283
40. Antonarakis ES, Park SH, Goh JC, Shin SJ, Lee JL, Mehra N, et al. Pembrolizumab plus olaparib for patients with previously treated and biomarker-unselected metastatic castration-resistant prostate cancer: the randomized, open-label, phase III KEYLYNK-010 trial. J Clin Oncol. 2023;41(22):3839-50. https://doi.org/10.1200/JCO.23.00233
41. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23. https://doi.org/10.1056/NEJMoa1213755
42. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol. 2002;168(6):2439-43. https://doi.org/10.1016/S0022-5347(05)64163-8
43. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14(6):1756-64. https://doi.org/10.1200/JCO.1996.14.6.1756
44. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-22. https://doi.org/10.1056/NEJMoa1001294
45. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879-82. https://doi.org/10.1093/jnci/djh141
46. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med. 2009;361(8):745-55. https://doi.org/10.1056/NEJMoa0809003
47. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377(9768):813-22. https://doi.org/10.1016/S0140-6736(10)62344-6