ASCO® Guidelines

Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update			
Recommendations	**Type**	**Evidence Quality**	**Strength**
1.0. (Updated) Docetaxel, abiraterone, enzalutamide, apalutamide, or darolutamide each when administered with ADT, represent five separate standards of care (SOCs) for noncastrate metastatic prostate cancer. With the exception of the triplet therapies of docetaxel plus abiraterone plus ADT and docetaxel plus darolutamide plus ADT, the use of any of these agents in any other particular combination or in any particular series cannot yet be recommended.	EB	-	S
1.1. (Updated) For patients with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED[1] (four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease) who are candidates for treatment with chemotherapy but are unwilling or unable to receive triplet therapy (e.g. due to insurance constraints), docetaxel plus ADT should be offered.	EB	H	S for patients with HVD
Practical Information for Recommendation 1.1. (Updated) *Patients should be made aware that doublet therapy (docetaxel plus ADT) has proven inferior OS compared to triplet therapy, such as abiraterone and prednisone plus docetaxel plus ADT.*			
1.11. (Updated) For patients with de novo metastatic noncastrate prostate cancer with high-volume disease as defined per CHAARTED[1] who are being offered ADT plus docetaxel chemotherapy, triplet therapy (abiraterone and prednisone plus ADT and docetaxel), should be offered per PEACE-1.[2] Abiraterone and prednisone plus ADT and docetaxel demonstrated significant OS and radiographic progression-free survival benefits compared to ADT and docetaxel alone for patients with high-volume disease.	EB	H	S for patients with HVD as defined per CHAARTED[1]
Practical Information for Recommendation 1.11. (Updated) *OS data for patients with low-volume de novo metastatic noncastrate prostate cancer from PEACE-1[2] are still too immature to justify recommending abiraterone-based triplet therapy (abiraterone and prednisone plus ADT and docetaxel).*			
1.15. (Updated) For patients with de novo metastatic noncastrate prostate cancer who are being offered ADT plus docetaxel chemotherapy, triplet therapy (darolutamide plus ADT and docetaxel) should be offered per ARASENS.[3] Compared to placebo plus ADT and docetaxel, darolutamide plus ADT and docetaxel demonstrated significant OS benefits, in addition to significantly longer times to castration-resistant prostate cancer, pain progression, first skeletal event, and initiation of subsequent systemic antineoplastic therapy.	EB	H	S

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1.16. (Updated) The recommended regimen for patients with metastatic noncastrate prostate cancer treated with darolutamide, docetaxel and ADT is darolutamide (600 mg as two 300 mg tablets orally with food) twice daily (to a total daily dose of 1200 mg) with ADT. Docetaxel administration (75 mg/m^2) should begin within 6 weeks of the first dose of darolutamide. Docetaxel should be administered intravenously every 3 weeks for up to six cycles.	EB	H	S
Practical Information for Recommendations 1.15 & 1.16. (Updated) *Discussions with patients should include the cost of darolutamide treatment compared with other options such as abiraterone.*			
1.2. (Updated) For patients with low-volume metastatic disease (LVD) as defined per CHAARTED[1] who are candidates for chemotherapy, docetaxel plus ADT should not be offered due to lack of sufficient evidence.	EB	H	S for patients with LVD
1.3. (Updated) For patients with metastatic noncastrate prostate cancer treated with docetaxel, the recommended regimen is six doses administered at 3-week intervals at 75 mg/m^2 either alone (per CHAARTED[1]) or with prednisolone (per STAMPEDE).[4]	EB	H	S
Practical Information for Recommendation 1.3. (Updated) • *The strongest evidence of benefit for docetaxel is for those patients who were diagnosed with de novo metastatic disease or HVD (defined per CHAARTED[1] as four or more bone metastases, one or more of which is outside of the spine or pelvis, and/or the presence of any visceral disease). The criteria apply independent of the presence or absence of nodal disease.* [5] • *Patients with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an OS benefit is not compelling for patients who do not have de novo metastatic disease and/or who do not meet the HVD criteria.* [5] *Long-term survival data from CHAARTED[1] and a post hoc aggregated analysis of CHAARTED and GETUG-AFU-15 data only showed an OS benefit for patients with HVD and de novo metastases. There was no OS benefit for LVD, irrespective of whether the patients had metastases at diagnosis or after failure of prior local therapy.*[6] *Clarke et al[7] re-examined OS by disease burden using STAMPEDE data with longer follow-up, but the analysis had inadequate statistical power (<80%) to detect an OS difference by disease burden if in fact one existed.* • *As a chemotherapy agent, docetaxel is associated with somewhat greater toxicity than androgen-targeted therapies (novel hormone therapies), but the treatment course is relatively short (limited to 6 cycles), much less costly and generally covered by insurance, hence reducing the financial toxicity.*			

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Recommendations	**Type**	**Evidence Quality**	**Strength**
1.4. For patients with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE.[8]	EB	H	S for patient with high-risk disease as defined per LATITUDE[8]
1.5. For patients with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE.[9]	EB	H	M for patients with low-risk disease per STAMPEDE[9]
1.6. The recommended regimen for patients with metastatic noncastrate prostate cancer is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until progressive disease is documented.	EB	H	S
1.7. (Updated) ADT plus enzalutamide should be offered to patients with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as RP or RT for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (PSA progression-free, clinical progression-free, and overall) when compared with ADT alone for patients with metastatic noncastrate prostate cancer as a group per ENZAMET.[10] Enzalutamide also has long-term survival benefits overall, for those with low- or high-volume disease, and those with low- or high-volume disease and no docetaxel use.[11] Per ARCHES,[12] enzalutamide significantly improved time to first subsequent antineoplastic therapy in addition to survival benefits overall and among those with high volume disease, no prior docetaxel and previous use of ADT or orchiectomy.[12]	EB	H	S
1.8. (Updated) The recommended regimen for patients with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT.	EB	H	S
Practical Information for Recommendation 1.8. (Updated) *Discussions with patients should include the cost of enzalutamide treatment compared with other options, such as abiraterone.*			
1.9. ADT plus apalutamide should also be offered to patients with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as RP or RT for localized disease per TITAN.[13]	EB	H	S
1.95. The recommended regimen for patients with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT.	EB	H	S

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Practical Information for Recommendations 1.9 and 1.95. (Updated) • *Discussions with patients should include the cost of apalutamide treatment compared with other options, such as abiraterone.*			
2.1. ADT plus abiraterone and prednisolone should be considered for patients with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failure-free survival benefit per STAMPEDE.[9] RT to the primary was mandated in STAMPEDE[9] for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, DP, or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for 2 or less years to patients with nonmetastatic disease.	EB	H	S
2.2. In resource-constrained settings where drugs such as abiraterone may not be available, combined androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide, may be offered to patients with locally advanced nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses.	EB	H	M
Practical Information for Recommendation 2.2. *For patients with high-risk nonmetastatic prostate cancer progressing after RP or RT or both, it is currently unclear whether enzalutamide (160 mg) plus leuprolide improves metastasis-free survival compared with enzalutamide monotherapy or placebo. Although recruitment is complete for the ongoing phase III EMBARK trial, which is designed to answer this question, results are not yet available. Thus, no recommendation can be made at this time.*			
3.1. Early (immediate) ADT may be offered to patients who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo RT based on evidence in one meta-analysis of a modest, but statistically significant benefit in terms of both OS and cancer-specific survival among the larger population of patients with locally advanced nonmetastatic disease.	EB	I	M
Practical Information for Recommendation 3.1 • *Discussions with patients regarding early ADT should include the risk of short- and long-term side effects. Deferred ADT is often preferred by patients who desire to avoid, or at least delay, potential ADT side effects. Consideration should be given to restricting deferred ADT to those patients who are asymptomatic.* • *No recommendation can be provided at this time for patients with PSA relapse after local treatment. Although existing studies suggest a potential OS benefit, additional research is needed as such studies were underpowered.*			

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4.1. Intermittent therapy may be offered to patients with high-risk biochemically recurrent nonmetastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the noninferiority of IADT when compared with CADT with respect to OS.[14] This is further supported by evidence from four meta-analyses[15-18] testing superiority. Low-risk biochemical recurrence after RP is defined as a PSA doubling time < 1 year and pathologic Gleason score < 8. Low-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence > 18 months and clinical Gleason score < 8. High-risk biochemical recurrence after RP is defined as a PSA doubling time < 1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence < 18 months or a clinical Gleason score of 8-10.[19] Active surveillance may be offered to patients with low-risk biochemically recurrent nonmetastatic prostate cancer.	EB	H	S
Practical Information for Recommendation 4.1. • *Although patients with noncastrate de novo metastatic prostate cancer were included in the studies reviewed for this clinical question, alternative standard-of-care therapies with proven survival benefits now exist, as outlined in Recommendation 1 to include ADT plus docetaxel, ADT plus abiraterone, ADT plus enzalutamide, or ADT plus apalutamide. Similar support for these existing SOCs does not universally exist for patients with LVD or those who develop M1 disease after prior local therapy, and further research is needed. No specific additional recommendation with respect to the use of IADT in the noncastrate metastatic prostate cancer population was possible at this time because IADT has not been studied in combination with additional cytotoxic or hormonal agents in this population.* • *Patients considering IADT should be made aware of the potential benefits of IADT associated with the off-treatment intervals, such as reduced treatment side effects, quality-of-life benefits, and lower cost. As patients on IADT require close follow-up, they must be motivated to adhere to frequent doctor visits for monitoring, even during off-treatment periods.*			

Abbreviations. ADT, androgen deprivation therapy; CADT, continuous androgen deprivation therapy; DP, disease progression; EB, evidence based; FDA, U.S. Food and Drug Administration; H, high; HVD, high-volume disease; I, intermediate; IADT, intermittent androgen deprivation therapy; LVD, low-volume metastatic disease; M, moderate; OS, overall survival; PSA, prostate-specific antigen; RP, radical prostatectomy; rPFS, radiographic progression-free survival; RT, radiotherapy; S, strong; SOCs, standards of care; -, no evidence available

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