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Triplet Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Updates on treatment recommendations from the American Society of Clinical Oncology Genitourinary Cancers Symposium, 2023

Androgen deprivation therapy (ADT) alone is not considered sufficient for treating metastatic hormone-sensitive prostate cancer (mHSPC)[1]

Should triplet therapy—involving ADT, a chemotherapeutic (docetaxel), and an androgen receptor axis-targeted therapeutic agent (darolutamide or abiraterone)—be prescribed as the standard of care for all cases of mHSPC?

Investigators of the **ARASENS and PEACE-1** trials sought to find an answer to this

Findings from the trials[1]

Patients' overall survival (OS) improved, but treatment should factor:

- Occurrence: *De novo*/recurrent
- Race/Ethnicity
- Mutational analysis
- Patient preference and performance
- Risk status
- Disease burden: Low/high

Addressing disease volume and risk can provide more information to clinicians

ARASENS subgroup analysis: Assessing efficacy and safety of darolutamide (DARO) + ADT + docetaxel (DOC)[2]

mHSPC classification

High-risk disease (LATITUDE trial) ≥2 risk factors

- Gleason score (GS) ≥ 8
- ≥3 bone lesions
- Presence of measurable visceral metastasis

High-volume disease (CHAARTED trial)

- Visceral metastases
- ≥4 bone metastases

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What was the effect of DARO + ADT + DOC treatment on clinical outcomes?[2]

Risk of death reduced by **32.5%**

Prolonged OS across disease groups, with hazard ratio (HR) for death being:

High-volume 0.69	Low-volume 0.68
High-risk 0.71	Low-risk 0.62

HRs for progression to metastatic castration-resistant prostate cancer (mCRPC) across disease groups:

High-volume 0.41	Low-volume 0.21
High-risk 0.38	Low-risk 0.32

Treatment emergent adverse events (AE) matched across high-/low-volume and risk subgroups[2]

- Mental impairment
- Depressed mood
- Hypertension
- Seizures
- Weight loss
- Cerebral ischaemia
- Breast disorders/ Gynaecomastia
- Fatigue
- Diabetes mellitus/ Hyperglycaemia
- Vasodilation/ Flushing
- Rashes
- Falls
- Bone fractures
- Cardiac disorders

How effective is triplet therapy in elderly patients with mHSPC?[3]

Efficacy and safety profile of treatment regimen involving

Standard of care (SOC): ADT +/- DOC

+ Abiraterone acetate + prednisone (AAP) | Radiotherapy (RXT) | AAP + RXT

Determined in men ≥ 70 years old (older men) and < 70 years old (younger men)

Effects in older vs. younger men[3]

Altered performance status per Eastern Cooperative Oncology Group Scale (Grade: 1–2)
36% vs. 26%

Increased:

- Hypertension
  56.5% vs. 38.2%
- Diabetes mellitus type 2
  15.5% vs. 11%
- AAP OS benefit
  HR = 0.80 vs. 0.71
- Grade 3–5 adverse events (AE)
  69% vs. 61%

Decreased:

- Use of DOC
  66% vs. 51%
- Benefit of AAP on radiographic progression-free survival (rPFS; overall population)
  HR = 0.65 vs. 0.49
- OS (overall population)
  HR = 0.95 vs. 0.73

No difference/comparable:

- Visceral disease
- GS
- Tumour volume
- Protein-specific antigen (PSA)
- Benefit of AAP on rPFS when administered with ADT+DOC
  HR = 0.55 vs. 0.5
- AE in patients not receiving AAP
  48% vs. 47%

Is it appropriate to use triplet therapy in older patients?[3]

Unless fit, older men benefit less from AAP + ADT + DOC therapy
Deteriorating performance status and comorbidities influence reduced benefit
Healthy older men require:

- Geriatric assessment
- Close monitoring for complications

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What role does DOC have in triplet therapy moving forward?[1]

At 84 months following treatment with AAP + ADT

Patient survival **79%** among those with high-risk M0

63% among those with M1 low volume

34% among those with M1 high volume

Meta-analysis of CHAARTED, GETUG, and STAMPEDE data revealed that the DOC cohort had:

- Heterogenous response depending on volume and timing of M1 diagnosis
- Heterogenous response depending on volume and CT stage
- Greatest benefit in high-volume disease
- Significant improvements in quality of life

Planning treatment based on mHSPC disease progression[1]

Progression

- Consider abiraterone or enzalutamide
- Consider poly-ADP ribose polymerase inhibitors (PARPi) depending on homologous recombination repair gene mutations

ADT monotherapy	Triplet therapy (ADT + DOC + ARPI)
ADT + chemotherapy (DOC)	ADT + androgen receptor pathway inhibitors (ARPI)

Progression

- Consider Lu-prostate-specific membrane antigen radioligand therapy
- Consider chemotherapy
- Consider PARPi depending on homologous recombination repair mutations (HRRm)

Progression

- Consider chemotherapy
- Consider PARPi depending on HRRm

Considerations for mHSPC treatment

- Clinical trials evaluating triplet therapy in mHSPC show a favourable safety profile
- Older men, if healthy and slated for triplet therapy, should receive a geriatric assessment and regular monitoring for complications
- Developing predictive/prognostic tests and identifying biomarkers is necessary to determine which patients can benefit from DOC treatment
- Choice of treatment following progression to mHRPC should be tailored based on a patient's health status and needs

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3. Mourey, L., Boyle, H. J., Roubaud, G., McDermott, R. S., Supiot, S., Tombal, B. F., ... & Carles, J. (2023). Efficacy and safety of abiraterone acetate plus prednisone and androgen deprivation therapy+/-docetaxel in older patients (≥70 years), with de novo metastatic-castration sensitive prostate cancer, compared to younger patients (<70 years): The PEACE-1 trial. Presented in: 2023 Genitourinary (GU) American Society of Clinical Oncology (ASCO) Annual Meeting, San Francisco, Feb 16–18, 2023.
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