Management of Castrate Resistant Prostate Cancer (CRPC): An update

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Management of Castrate Resistant Prostate Cancer (CRPC): An update

• Definition Of CRPC
• First line treatment in mCRPC
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  - Enzalutamide PREVAIL Study
  - Docetaxel
  - Sipuleucel T
• Second line treatment in mCRPC
  - Salvage Chemotherapy Docetaxel or Cabazitaxel
  - Abiraterone COU-AA-301 trial
  - Enzalutamide AFFIRM study
  - Bone targeted therapies in mCRPC

Treatment of M0 CRPC
  - APA (SPARTAN trial)
  - ENZA (PROSPER trial)
CRPC
Definition

Serum testosterone < 50 ng/dL

Plus either;

Biochemical progression: 3 consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, with PSA > 2 ng/mL

or

Radiological progression: ≥ 2 new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours)

Follow-up after hormonal treatment

- Patients should be evaluated at 3-6 m after the initiation of treatment.
- Serum PSA, Serum testosterone, Routine Lab (liver function, S.C, Hb, Alk Ph....etc)

Clinical follow-up: is mandatory.
Neither biochemical nor imaging modalities can replace face to face clinic visits.

Of upmost importance in patients in the M1b stage is to highlight and check for possible early signals of spinal cord compression, urinary tract complications.
CRPC: Metastatic Vs non metastatic

PSA surveillance has resulted in earlier detection of progression

In such patients, occult micro-mets might exist, but undetectable (M0)

33% will develop bone mets within 2 y,

Until Recently, there were no available studies suggesting a benefit for treatment for M0CRPC.

Murray NP, et al. Bone Marrow Res 2012;259351
continued ADT in CRPC is debatable

These data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on LHRH analogues.

However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment.

CRPC, Treatment

- Until recently, there was no evidence for treatment of non-metastatic CRPC outside a clinical trial.

- Patients with CRPC should be counseled, managed and treated by a multidisciplinary team.
first-line treatment of mCRPC

1- Abiraterone COU-AA-302 Trial,

2- Enzalutamide PREVAIL Study

3- Docetaxel

4- Sipuleucel T
first-line treatment of mCRPC

**Abiraterone**

**COU-AA-302 Trial,**

1,088 chemonaïve mCRPC patients were randomised to abiraterone acetate and placebo, both combined with prednisone.

Patients were mCRPC,

- ECOG performance status 0 or 1
- Asymptomatic or mildly symptomatic.

first-line treatment of mCRPC

Abiraterone

With a median follow-up of 49.4 m

Significant radiological PFS (median 16.5 vs. 8.2 m, p < 0.001)

OS was 34.7 vs 30.3 months (p = 0.0027)

Side effects related to mineralocorticoids and liver function were more frequent with abiraterone (fluid retention, oedema or hypokalaemia).

Update of COU-AA-302 Study:  
**Stratified Analysis Based on Pain, PSA and Gleason Score**

All patients achieved significantly improved outcomes with AA + P versus Placebo, including *OS and rPFS*

- Greater benefit observed with AA + P versus Placebo alone in patients low baseline PSA and prostate cancer-related pain than to Gleason score

- Initiation of AA + P at a time point when patients do not have significant pain or pronounced PSA elevation may be associated with greater clinical benefits

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*Miller K, et al. Poster (#775), 31st Annual EAU Congress, 11-15 March 2016, Munich, Germany*
first-line treatment of mCRPC
Enzalutamide

*PREVAIL Study*

In a chemonaïve population of 1717 men

- Decrease in PSA by > 50% in 78% of patients
- A significant improvement in time to radiological progression ($p < 0.0001$)
- Statistical improvement in OS ($p < 0.001$).
- The most common clinically relevant adverse events were fatigue and HTN.

first-line treatment of mCRPC

Docetaxel

A significant improvement in median OS of 2-2.5 m occurred with docetaxel-compared to mitoxantrone + prednisone therapy

Docetaxel is the standard for first-line cytotoxic chemotherapy

first-line treatment of mCRPC

**Docetaxel**

Palliation was the main target. The patients considered for docetaxel represent a heterogeneous population.

Several poor prognostic factors have been described, such as a PSA level > 114 ng/mL, or the presence of visceral met
first-line treatment of mCRPC

Sipuleucel T

Sipuleucel T is an active cellular immunotherapy agent fused to granulocyte-macrophage colony-stimulating factor

In 2010, a phase III trial of Sipuleucel T showed a survival benefit in 512 CRPC patients
first-line treatment of mCRPC

Sipuleucel T

After a median follow-up of 34 m, the median OS was 25.8 m compared to 21.7 m in the placebo group ($P = 0.03$).

PFS was equivalent in both arms (14 weeks).

Surprisingly, no PSA decline was observed

mCRPC

Second line treatment

• Salvage Chemotherapy  Docetaxel or Cabazitaxel

• Abiraterone, *COU AA 301 Trial*

• Enzalutamide, *the AFFIRM Study*

• Bone targeted therapies in mCRPC
mCRPC: Second line treatment

- The timing of second-line treatment remains unclear in mCRPC, although it is clearly advisable to **start immediately in symptomatic men**.

- it is not clear how to choose the first “second-line” treatment

- ECOG performance status was used to stratify patients. Generally men with a performance status of 0-1 are **likely to tolerate** treatments and those with performance status of 2 or more are **less likely** to benefit.
mCRPC: Second line treatment
Abiraterone acetate, COU-AA-301 trial.

- 1,195 patients were randomised to AA or placebo.
- All patients had progressive disease after docetaxel therapy

- Significant median OS (15.8 m vs 11.2 m in the placebo arm, \( p < 0.001 \)).
- PSA, radiologic tissue response, time to PSA progression, in favour of AA

- Mineralocorticoid-related SE were more in the AA group

mCRPC: Second line treatment
Enzalutamide (The AFFIRM study)

1,199 patients. The patients had progressed after docetaxel treatment,

Significant median OS (18.4 m Vs 13.6 m, p < 0.001).
PSA, soft tissue response, QoL, time to PSA or objective progression were in favour of enzalutamide.

There was a 0.6% incidence of seizures in the enzalutamide group.

CRPC: Second line treatment

Docetaxel.

Intermittent docetaxel re-treatment in patients who had clearly responded to first-line docetaxel.

PSA response can be achieved in about 60% of patients with a median PFS of 6 months.

Treatment-associated toxicity is minimal and similar to that of first-line docetaxel.


mCRPC: Second line treatment
Cabazitaxel TROPIC trial

- **OS benefit** (15.1 vs. 12.7 m, p < 0.0001)
- Significant improvement in **PFS** (2.8 vs. 1.4 m, p < 0.0001),
- Objective response rate according to **RECIST** criteria (14.4% vs. 4.4%, p < 0.005),
- **PSA response** rate (39.2% vs. 17.8%, p < 0.0002).
- Side effects more in the cabazitaxel arm, haematological and non-haematological

*de Bono JS, et al. Lancet 2010 Oct;376(9747):1147-54*

mCRPC: Second line treatment
Cabazitaxel TROPIC trial: an update

• Patients who were on statins had a slightly longer median OS but no difference in PSA PFS or rPFS

• The study is not a prospective randomized one

Lorente D. et al. ESMO 2018, Munich, Germany.
Bone targeted therapies

CRPC with painful bone metastases, external beam radiotherapy is highly effective. Bisphosphonates

Radium 223 (alpharadin) a large phase III trial (ALSYMPCA),

- fewer SREs
- longer time to first SRE
- be highly effective in reducing bone pain.

Treatment of non metastatic CRPC (M0)

- Apalutamide (SPARTAN trial)
- Enzalutamide (PROSPER trial)
SPARTAN: A Study of Apalutamide in Men with M0 CRPC

• 1,207 patients
• Men were randomized to either APA 240 mg daily + ADT or placebo + ADT.

Primary endpoint: Metastasis-free survival (MFS).

Secondary endpoints

• Time to metastases
• Progression-free survival
• Time to symptomatic progression
• Overall survival
• Time to cytotoxic chemotherapy
• PFS-2 (defined in study design)
• Time to PSA progression

Small E J, ASCO-GU 2018: San Francisco, CA
SPARTAN: A Study of Apalutamide in Men with M0 CRPC

- MFS: there was a 72% risk reduction in MFS favoring apalutamide.
  \[(40.5 \text{ m vs. } 16.2 \text{ m for placebo})\]

Similar findings were identified for all secondary endpoints – again this was a hierarchical analysis

Overall survival was an interim analysis, but there was already early evidence of benefit.
SPARTAN: A Study of Apalutamide in Men with M0 CRPC

- PFS2 analysis was unique to the SPARTAN trial.

- 53% who discontinued apalutamide and 78% who had discontinued placebo received subsequent therapy for mCRPC (primarily AA through the trial).

Interestingly, men who had been treated with APA had a 51% risk reduction in PFS2 compared to men treated with placebo (p<0.0001). While not powered for this analysis, this highlights the fact that maybe early treatment of cM0 CRPC may help improve subsequent management of mCRPC and delay failure of therapy.
In terms of adverse events, APA was well tolerated. Grade 3-4 Adverse events were slightly higher in the APA arm (45\% vs. 34\%), as were serious adverse events (25\% vs. 23\%).

Treatment discontinuation due to adverse events (11\% vs. 7\%) was also slightly higher in the APA arm. Importantly, seizures were rare, and were never Grade 3 or 4.
SPARTAN: A Study of Apalutamide in Men with M0 CRPC
Update of SPARTAN 2019

- APA was previously shown to result in an improvement in metastatic free survival (MFS) and symptomatic progression.

- With a median APA treatment duration of 25.7 m, APA continues to show significant benefit in PFS2 and safety profile remained unchanged

Enzalutamide in Men with M0CRPC (PROSPER Trial)

• Double-blind, phase 3 trial, A total of 1401 patients

• Patients randomly assigned, men with M0 CRPC who were continuing ADT to receive enzalutamide (at a dose of 160 mg) or placebo once daily.

• The primary end point was MFS (defined as the time from randomization to radiographic progression or as the time to death without radiographic progression).

• 23% in the enzalutamide group had metastasis or had died, as compared with 49% in the placebo group.

Enzalutamide in Men with M0CRPC (PROSPER Trial)

- Median MFS was **36.6 m** in the Enza gp Vs **14.7 m** in the placebo gp (**P<0.001**)

- The time to the first use of a subsequent antineoplastic therapy was longer with ENZA gp than with placebo (**39.6 vs. 17.7 m; P<0.001**).

- The time to PSA progression (**37.2 vs. 3.9 m; P<0.001**); progression occurred in **22% vs. 69%** of patients
Enzalutamide in Men with M0CRPC (PROSPER Trial)

• At the first interim analysis of overall survival, 103 patients (11%) receiving enzalutamide and 62 (13%) receiving placebo had died.

• Adverse events of grade 3 or higher occurred in 31% of the patients receiving ENZA, as compared with 23% of those receiving placebo.
PROSPER update 2019

• Longer Met Free survival with Enza
• Low pain level
• High health QOL

Tombal B. Lancet feb 2019
SPARTAN (APA) Vs PROSPER (ENZA)

- The PFS2 analysis was unique to the SPARTAN trial.

- Men who had been treated with apalutamide had a 51% risk reduction in PFS2 compared to men treated with placebo.

  this highlights the fact that maybe early treatment of cM0 CRPC may help improve subsequent management of mCRPC and delay failure of therapy.
CRPC: CONCLUSIONS

• Patients on ADT should be followed up meticulously
• CRPC should be diagnosed early
• Now, we have to treat Non metastatic CRPC
• Non metastatic CRPC should be treated as early as possible
• For mCRPC, we have many drugs which could be used
• Treatment of CRPC should be through a MDT
Thank you