
بسم الله الرحمن الرحيم

Enzalutamide vs Abiraterone in hormone sensitive metastatic prostate cancer

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Metastatic castration-sensitive prostate cancer

- at presentation
- after definitive treatment of localized disease
- isolated biochemical recurrence
- The majority of men in all three groups have not been receiving long-term ADT, and serum testosterone levels are typically >50 ng/dL. termed castration-sensitive prostate cancer

ADT

- The critical role of androgens in stimulating prostate cancer growth
  - in 1941 by Charles Huggins.
- These findings led to the development of ADT as the treatment for patients with advanced prostate cancer.
- Although ADT is palliative :
  - normalize PSA in over 90 % of patients
  - objective tumor responses in 80 to 90 %
  - improve QOL by :
    - reducing bone pain
    - as well as the rates of complications (eg, pathologic fracture, spinal cord compression, ureteral obstruction).

- For men with advanced CSPC, LA, NMCSPC, and MPC :
  - ADT is the mainstay of initial treatment.
- More recently, the development of additional effective systemic therapies has led to their use in combination with ADT for initial therapy of men with more advanced disease:
  - **Abiraterone/prednisone plus ADT**
  - **Docetaxel plus ADT**
  - **Enzalutamide or apalutamide plus ADT**

- Contemporary research has led to the development of multiple combined modality approaches for men with advanced NCPC that are associated with better outcomes than can be achieved with ADT alone.
- The goals of systemic therapy:
  - prolong survival
  - minimize complications
  - maintain QOL

combined modality approaches

- **Abiraterone/prednisone plus ADT** :
  - Abiraterone :
  - A structural analogue of pregnenolone and inhibits an enzyme necessary for androgen synthesis (CYP17) .
  - acts by blocking the intracellular conversion of androgen precursors in the testes, adrenal glands, and prostate tumor tissue
- It initially was shown to prolong OS in CRPC

❑ More recently, randomized trials showed that :

- ADT + abiraterone + prednisone in patients with very high-risk localized NMCSPC or MCSPC :
  - prolongs OS Vs ADT alone

combined modality approaches

- **Enzalutamide or apalutamide plus ADT** :
  - Both enzalutamide and apalutamide :
    - androgen receptor inhibitors
- Both drugs have significant activity in men with CRPC
- More recently, three randomized trials:
  - ENZAMET (ANZUP)
  - TITAN
  - ARCHES

➢showed benefit over ADT alone for MCSPC

- Both apalutamide and enzalutamide are now approved for use in this setting

Abiraterone

- The toxicity profile of abiraterone :
- **hypertension and hypokalemia**.
- The effects of mineralocorticoid excess can be attenuated by coadministration with prednisone, which reduces ACTH-mediated stimulation of the adrenal glands.
- However, long-term combined treatment is associated with muscle wasting and weakness.
- fluid retention
- abnormal liver function tests

Enzalutamide TOXICITY

- the most common : headache
- Fatigue
- diarrhea
- hot flashes
- musculoskeletal pain
- ↓ WBC
- Seizures are infrequent, occurring in less than 1 percent of treated patients
- In addition, all treatments directed at the androgen receptor have adverse effects on other critical physiologic functions, including the cardiovascular system.

- Importantly, there are only limited clinical trial data comparing :
  - the combination of ADT plus abiraterone
  - versus
  - ADT plus docetaxel,
- and there are no data comparing ;
  - either of these approaches with ADT plus either apalutamide or enzalutamide.

- Given the lack of comparative data supporting one approach over any other:
- the choice of the specific regimen is usually based on ;
  - disease extent
  - potential toxicities associated with abiraterone, docetaxel, apalutamide, and enzalutamide
  - the expected duration and cost of treatment

Asco guidline

Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer

Patient with advanced*, metastatic, or recurrent prostate cancer with noncastrate levels of serum testosterone (>50 ng/dL)

Assess disease extent

Biochemical recurrence only after local therapy (RT or RP); local therapy optimized

Are high-risk features present?¶

- Yes → ADT monotherapy
- No → Options include:
  - Active surveillance (preferred)
  - ADT monotherapy

Locally advanced, nonmetastatic; is the patient willing/able to undergo RT?

- Yes → RT plus ADT plus abiraterone and prednisone△
- No → Early ADT monotherapy or surveillance with deferred ADT

Metastatic disease*; either de novo or recurrent. Is high-volume disease present?◊

- Yes → Options include:
  - ADT plus docetaxel
  - ADT plus abiraterone and prednisone△
  - ADT plus apalutamide
  - ADT plus enzalutamide
- No → Options include:
  - ADT plus abiraterone and prednisone△
  - ADT plus apalutamide
  - ADT plus enzalutamide

  Consider RT to prostate if previously untreated

The combination of ADT and abiraterone ASCO guidelines

- ❑In high-risk de novo MPC
- High-risk disease is defined by :
  - the presence of at least two of three factors:
    - GS ≥8,
    - at least three bone lesions
    - measurable visceral disease
- ❑may also be considered for :
  - low-risk metastatic disease
  - locoregional nonmetastatic disease

The combination of ADT and enzalutimide ASCO guidelines

- ADT + either apalutamide or enzalutamide :
  - in de novo MPC, regardless of disease extent
- apalutamide + ADT :
  - improvement in PFS and OS in high-volume metastatic disease
  - improvement in PFS in low-volume metastatic disease
- The benefits of adding enzalutamide to ADT :
  - in both high- and low-volume metastatic disease

UPTODATE(ADT plus other agents)

- For men with CSPC, high-risk or high-volume :
  - ADT + either abiraterone, docetaxel, apalutamide, or enzalutamide, rather than ADT alone
- for patients with low-risk or low-volume MPC
  - ADT + either abiraterone, apalutamide, or enzalutamide

Abiraterone

- More recently, at least two randomized trials showed that combining ADT with abiraterone plus prednisone in patients with very high-risk localized nonmetastatic or metastatic castration-sensitive disease prolongs OS compared with ADT alone

LATITUDE trial

- 1199 men with newly diagnosed CSMPC cancer were randomly assigned :
  - to ADT plus abiraterone and prednisone
  - or
  - to ADT plus matching placebos
- All men had high-risk disease with the presence of ;
  - at least two of three high-risk parameters:
    - Gleason score ≥8,
    - at least three bone lesions, and the presence of measurable visceral metastasis
- At a median follow-up of 52 months :
  - OS, the primary endpoint of the study, was significantly increased with the addition of abiraterone + prednisone
  - (MS 53.3 Vs 36.5 months, HR 0.66, 95% CI 0.56-0.78).

LATITUDE trial

- A similar degree of benefit was seen in all secondary endpoints, including :
  - time to pain progression
  - time to PSA progression
  - time to symptomatic skeletal event
  - time to chemotherapy
  - time to subsequent prostate cancer therapy
- and this was reflected in patient-reported outcomes showing clinical benefit in terms of symptoms and health-related QOL.
- The addition of abiraterone increased :
  - the rates of grade 3 or higher hypertension (21 Vs 10 %)
  - hypokalemia (12 Vs 2 %)

STAMPEDE trial

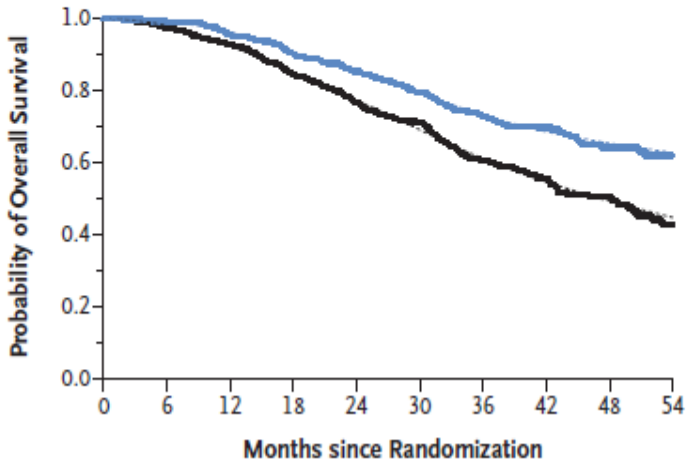
- 1917 men not previously treated with ADT were randomly assigned to :
  - ADT + abiraterone and prednisolone
  - ADT alone
- The patient population was heterogeneous and included the following groups:
  - Newly diagnosed patients constituted 94.9 percent of the study population.
    - These included high-risk prostate cancer :
    - (stage T3-T4N0M0 disease with either PSA ≥40 ng/mL or GS 8 to 10) in 26.6 percent
    - node-positive nonmetastatic disease (N1M0) in 19.2 percent
    - metastatic disease (M1) in 49.1 percent
- Prostate RT was mandated for men with newly diagnosed node-negative nonmetastatic disease, and encouraged in those with newly diagnosed node-positive nonmetastatic disease.

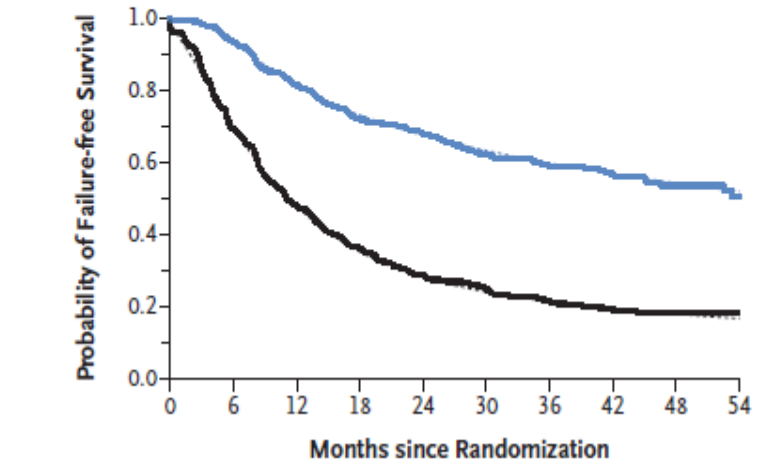
STAMPEDE t

- The primary endp
- coprimary endpoi
- at a median follov
- OS was **signific** survival 83 Vs 76 %
- Results were simil 0.75 and 0.61, res
- FFS was also **sigr** rate 75 Vs 45 % fo
- Improvement in FF
  - metastatic disease
  - locally advanced nonmetastatic disease

No. of Patients (no. of deaths)									
Combination therapy	960	(26)	917	(63)	840	(67)	541	(25)	161
ADT alone	957	(37)	909	(88)	806	(92)	491	(36)	123

No. of Patients (no. of treatment-failure events)									
Combination therapy	960	(104)	837	(75)	737	(52)	477	(14)	141
ADT alone	957	(319)	625	(140)	476	(56)	284	(18)	62





Dosing of abiraterone

- The approved dose of abiraterone :
  - 1000 mg orally,
  - once daily
  - on an empty stomach,
  - either one hour before or two hours after a meal.

Dosing of abiraterone

- A randomized phase II trial:
  - comparing the effects of 1000 mg per day fasting
- VS
  - 250 mg per day given after a low-fat breakfast

❑ demonstrated :

- similar PSA response
- PFS
- and pharmacodynamic effects with the lower dose

Dosing of steroids with abiraterone

- The concurrent use of glucocorticoids:
  - For metastatic CSPC, prednisone (5 mg daily)(LATITUDE)
  - prednisolone (5 mg daily) STAMPEDE)
- For MCRPC, a higher dose of prednisone (5 mg twice daily)

ADT plus second-generation antiandrogens

- Enzalutamide and apalutamide :
- ENZAMET [Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) 1304]
- TITAN, and ARCHES)
- showed :
  - benefit for ADT plus either enzalutamide or apalutamide over ADT alone for MCSPC

The ENZAMET (ANZUP 1304) trial

- randomly assigned 1125 MCSPC to:
  - ADT + either enzalutamide (160 mg daily)
  - or
  - bicalutamide, nilutamide, or flutamide until clinical disease progression or prohibitive toxic effects
- Notably, after enrollment of the first 88 patients, a protocol amendment permitted initiation of early treatment with 18 weeks of docetaxel at the discretion of the treating clinician.
- Early docetaxel was planned for a similar minority of men in either group (45 versus 44 percent in the enzalutamide and standard care arms, respectively).

ENZAMET

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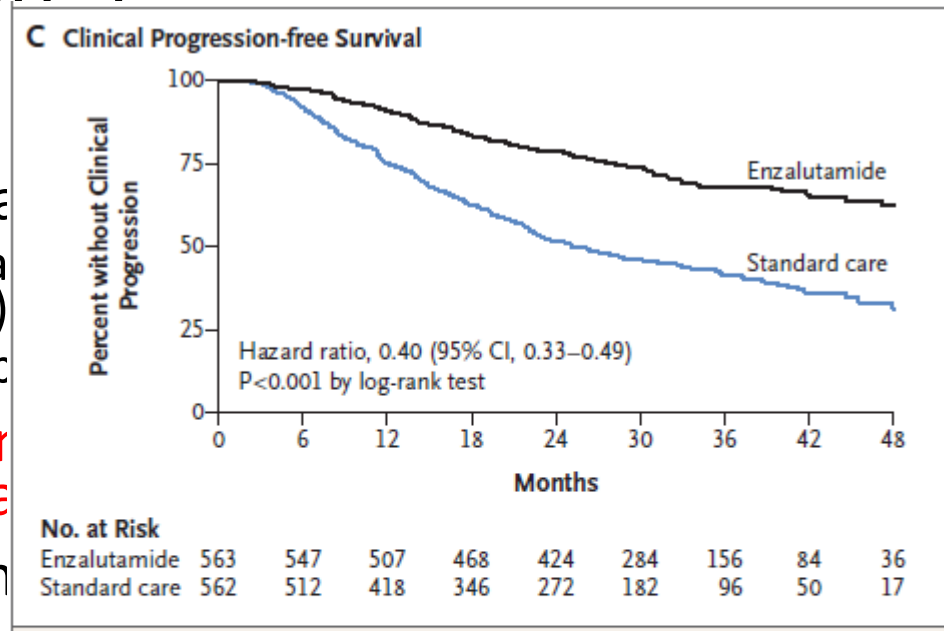
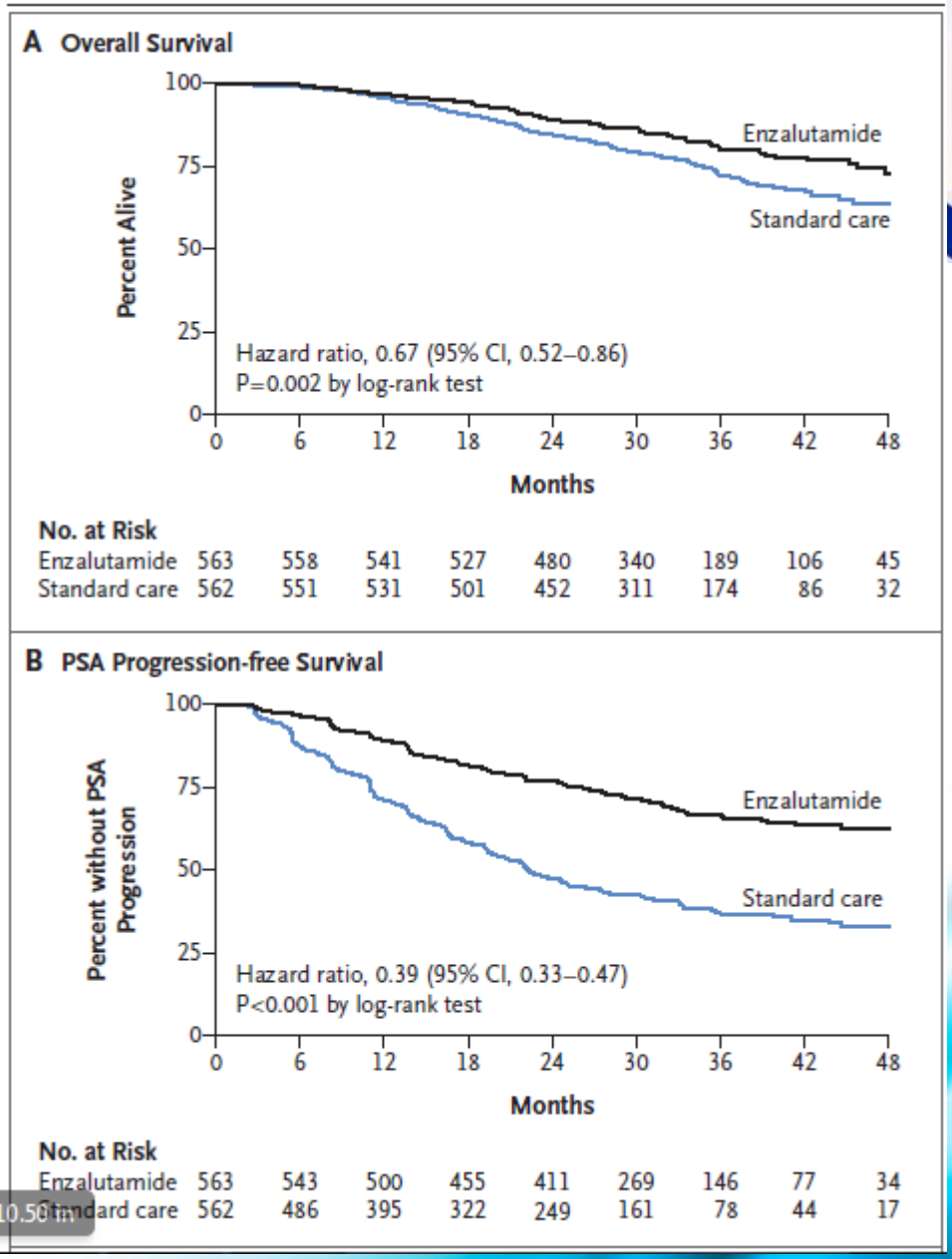


Figure 1. Overall Survival, PSA Progression-free Survival, and Clinical Progression-free Survival.

Among the patients who received enzalutamide and those who received standard nonsteroidal antiandrogen therapy (standard-care group), shown are Kaplan–Meier curves for overall survival (Panel A), progression-free survival as determined by the prostate-specific antigen (PSA) level (Panel B), and clinical progression-free survival as determined by results on imaging, symptoms, signs, or changes in therapy (Panel C).



ARCHES trial

- in the multicenter phase III ARCHES trial
- 1150 men with MCSPC were randomly assign
- **ADT + either enzalutamide 16**
- At a median follow-up of 14.4 months
  - combined therapy was associated with a primary endpoint, HR 0.39, 95% CI 0.30-0.
  - time to PSA progression (HR 0.19, 95% CI 0.1
  - **time to initiation of a new antin**
- benefit was observed in both high-volu ior docetaxel therapy
- The median treatment duration was 12.8 mon
- OS data were not yet mature.
- There were no significant differences in the frequency of g or nts between the groups.
- Largely based on these data, in December 2019, enzalutan s approved for men with metastatic CSPC

In a later analysis, the addition of enzalutamide + ADT delayed deterioration in several health-related QOL subscales and pain severity in high-volume disease

conflicting data on the benefit of combining Ttreatment

- There are conflicting data on the benefit of combining docetaxel plus either abiraterone or enzalutamide:
- The ENZAMET trial described no additional benefit when enzalutamide was added to docetaxel and ADT, and it was associated with more docetaxel toxicity

PSA progression alone should generally not be the sole reason to change therapy in castration-sensitive prostate cancer. Conventional imaging should be used to assess radiographic progression before making changes to the treatment approach. Assessment strategies during treatment for castration-sensitive prostate cancer are the same as for castration-resistant prostate cancer and are discussed in more detail separately.

systematic review

- Indian J Urol. 2021 Jul-Sep; 37(3): 288–290.
- Published online 2021 Jul 1. doi: 10.4103/iju.IJU_547_20

❑systematic review and network meta-analysis:

- compared the efficacy of combination therapies in **mHSPC** using either docetaxel, abiraterone acetate, enzalutamide, or apalutamide in addition to ADT

systematic review in the *European Urology* 2020(Sathianathen *et al.)*

- A network meta-analysis is a statistical method to compare :
  - the indirect evidence of multiple treatment options when a direct head to head comparison is lacking.
  - This is different from a meta-analysis which combines data of several studies comparing the same treatments
  - The objective of this network meta-analysis was to prove the superiority of one of the combination approach over the other, as head-to-head trials are currently unavailable.

systematic review in the *European Urology* 2020(Sathianathen *et al.)*

- The primary end point :
  - compare the OS
- the secondary outcome :
  - and PFS was
- A subgroup analysis:
- assess the efficacy of these drugs in high and low-volume disease settings, respectively

systematic review in the *European Urology* 2020(Sathianathen *et al.)*

- Seven trials including three for docetaxel (GETUG-AFU 15, CHAARTED, and STAMPEDE),
- two for abiraterone (STAMPEDE and LATITUDE),
- and one each for enzalutamide (ENZAMET) and apalutamide (TITAN) were included in this network meta-analysis.

systematic review in the 2020(Sathianathen *et*

HR is defined as the chance of an event occurring in the treatment arm divided by the chance of the event occurring in the control arm.

- In all these trials, the combina
  be superior to ADT alone in ter
- Indirect comparisons between:
  - the combination therapies showed that all four therapies were statistically comparable with respect to OS
  - however, enzalutamide + ADT had the least hazard ratio (HR) and was **superior in delaying death** (HR for enzalutamide + ADT 0.53, 95% confidence interval [CI] 0.37–0.75
  - apalutamide 0.64, 95% CI 0.47–0.86
  - abiraterone 0.69, 95% CI 0.61–0.79
  - docetaxel 0.81, 95% CI 0.72–0.92

systematic review in the *European Urology* 2020(Sathianathen *et al.)*

- In the present comparative survival analysis, the drug with the least HR was the one that was the best in delaying death.
- SUCRA is a graphical representation to rank the various treatment options in a network analysis from the highest to lowest in the order of their efficacy.
- Each treatment option is given a number from 0 to 100. The higher the number, the higher is its efficacy and probability of being in one of the top ranks and vice versa

systematic review in the *European Urology* 2020(Sathianathen *et al.)*

- Subgroup analysis revealed that:
  - only enzalutamide had :
    - a superior OS as compared to ADT and had the least overall HR (0.38, 95% CI 0.20–0.68) for low-volume disease
    - For high-volume disease, although enzalutamide had the least HR (0.62, 95% CI 0.40–0.95),

  ❖no drug was statistically superior to the other in the terms of OS.

  ❖ **SUCRA analysis ranked enzalutamide as the best, with 84.2% probability in the low-volume and 54.4% probability in the high-volume disease.**

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- In terms of overall progression-free analysis :
  - although all the four drugs delayed progression as compared to ADT, enzalutamide and abiraterone were the preferred drugs over docetaxel and apalutamide.
- Thus, it could be concluded that :
  - although all the four drugs are statistically comparable in the terms of OS for mHSPC, enzalutamide was better than the other three in the terms of HRs, more so for the low-volume disease.

current network meta-analysis

- showed that :
  - enzalutamide was better at :
  - delaying death especially in the low-volume disease setting Advantages
  - a very good quality-adjusted survival (*cf*. docetaxel)
  - a clear advantage of avoiding additional steroids (*cf*. abiraterone).
- However, enzalutamide needs to be avoided in patients with :
  - peripheral neuropathy or seizures and,
  - as opposed to docetaxel, may not be a cost-effective option

Table 1

Comparing the advantages of disadvantages of using docetaxel, abiraterone, enzalutamide, and apalutamide in metastatic hormone-sensitive prostate cancer

Drug	Points in favor of use	Points against use
Docetaxel	Maximum evidence backup	Has not shown OS benefit in low-volume disease
	Fixed dosing	Avoided in cardiac patients and patients with immunosuppression
	Maximum cost-benefit ratio	
	Better performance status at treatment-naive stage	
	Better response in poorly differentiated tumors	
	Saving the other drugs for when docetaxel fails	
Abiraterone	Has shown OS benefit in both low-volume and high-volume disease	Adding steroids alongside the drug
	Oral daily dosing therapy	Avoided in patients with chronic liver disease
	Good quality of life	
Enzalutamide	Good quality-adjusted survival	Avoided in patients with peripheral neuropathy and seizures
	Suitable for frail patients	Not a cost-effective option
	Good toxicity profile	Not a preferred option in patients with visceral metastases
		Less evidence backup

Table 1

Comparing the advantages of disadvantages of using docetaxel, abiraterone, enzalutamide, and apalutamide in metastatic hormone-sensitive prostate cancer

	Better performance status at treatment-naive stage	
	Better response in poorly differentiated tumors	
	Saving the other drugs for when docetaxel fails	
Abiraterone	Has shown OS benefit in both low-volume and high-volume disease	Adding steroids alongside the drug
	Oral daily dosing therapy	Avoided in patients with chronic liver disease
	Good quality of life	
Enzalutamide	Good quality-adjusted survival	Avoided in patients with peripheral neuropathy and seizures
	Suitable for frail patients	Not a cost-effective option
	Good toxicity profile	Not a preferred option in patients with visceral metastases
		Less evidence backup
Apalutamide	Good quality-adjusted survival	Avoided in patients with peripheral neuropathy and seizures
	Suitable for frail patients	Not a cost-effective option
	Good toxicity profile	Not a preferred option in patients with visceral metastases
		Less evidence backup

Thus, future trials are needed to out rightly declare one drug as the clear winner, and till future evidence is available, a tailored treatment with a personalized approach is required in men with carcinoma prostate presenting with metastatic disease


Thank you for
your attention!!!