

# APCCC – 2019

## Basel Switzerland

### First-line mCRPC after Docetaxel or AR Pathway Inhibitor in mHSPC Setting

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# Disclosures

- Advisory Boards: Janssen, Clovis, Incyte, AstraZeneca, Amgen
- Research Funding: Bayer, Janssen, Ambry
- Education: UpToDate, Best Doctors

# Assignment

First line mCRPC after ADT/docetaxel or ADT/AR-pathway inhibitor

- Rapid progression on mHSPC therapy
- Abiraterone
- Enzalutamide
- Docetaxel/cabazitaxel
- PSA flare
- Steroids with abiraterone (Abiraterone without steroids)
- Abiraterone with food

There is Currently no prospective clinical trial data to guide Optimal selection of Rx for first line mCRPC after ADT/docetaxel or ADT/AR-inhibition

# Optimal Rx for first line mCRPC (after ADT/docetaxel/AR) depends on established drivers of tumor growth

- Adaption and selection of resistant clones
- AR-dependent, AR independent, AR null
- Heterogeneity
- Clinically available measures of tumor biology are limited by availability, validated predictive accuracy and therapeutic targets
- Examples of potentially actionable tumor alterations in mCRPC
  - Genomic Sequencing (SPOP, CDK12...), AR-V7, AR amplification, DDR alterations, MSH high
- DNA repair gene alterations (especially biallelic BRCA) should be determined early for consideration of PARP/Carboplatin/trials

# mCRPC after Docetaxel or AR Pathway Inhibitor in mHSPC: currently no prospective data to guide Rx

## **Clinical features to guide therapy selection**

- De novo metastatic disease (vs initial localized disease/local Rx)
- Location and amount of presenting mHSPC
  - Tumor burden (various definitions), presence of visceral (liver) disease
- Timing of progression to mCRPC
  - On or shortly after docetaxel, on abiraterone/enzalutamide
- PSA doubling time
  - Short PSA<sub>dt</sub> (1-3 months), aggressive disease with shorter survival

# Progression on or shortly after docetaxel: Consider chemotherapy/other over AR-pathway

- Consider evaluating for neuroendocrine/small cell features (tumor biopsy)
- Treatment options (not prioritized)
  - Cabazitaxel
  - Docetaxel/carboplatin, carboplatin/PARP inhibitor (esp. if DNA repair deficiency)
  - While AR-axis therapy can be considered tends not to work well (consider AR-V7 testing and use if AR-V7 negative)
  - Radium223, Lutecium177 (PSMA positive imaging)
  - Immunotherapy if MSI high (rare)
  - Clinical trials (mutation directed therapy)

# Favorable progression

=/> median on phase 3 trial or after 2 years AR-pathway therapy

## • After docetaxel for HSPC

- Docetaxel after docetaxel (for HSPCa)
- Cabazitaxel
- Abiraterone/enzalutamide
- Carboplatin/PARP inhibitor (if DNA known repair deficiency)
- Clinical trial

## • After abi/enza/apa for HSPC

- Docetaxel
- The alternative of abi/enza
- Sipuleucel-T
- Carboplatin/PARP inhibitor (if DNA known repair deficiency)
- Clinical trial

# PSA Flare: Observed with all mCRPC therapies

- Flare definitions vary in the literature (PSA and radiographic)
- Docetaxel – 20-30%
- Abiraterone - 6-11%
- Cabazitaxel – 8-30%
- Enzalutamide – less common, case reports

## **Take Home Message –**

1. Be aware of flare as a possibility
2. Inform patients of possibility of PSA flare
3. Avoid changing therapy during the time of possible PSA flare (approx first 3 months)

## References

Stella A, BJU Int 2008

Ueda Y, Clin GU Ca 2017

Burgio SC, Clin GU Ca 2015

Angelergues A, Eur J Ca 2014

Steroids with abiraterone will be covered by Dr Attard (session 7)

# Abiraterone without steroids

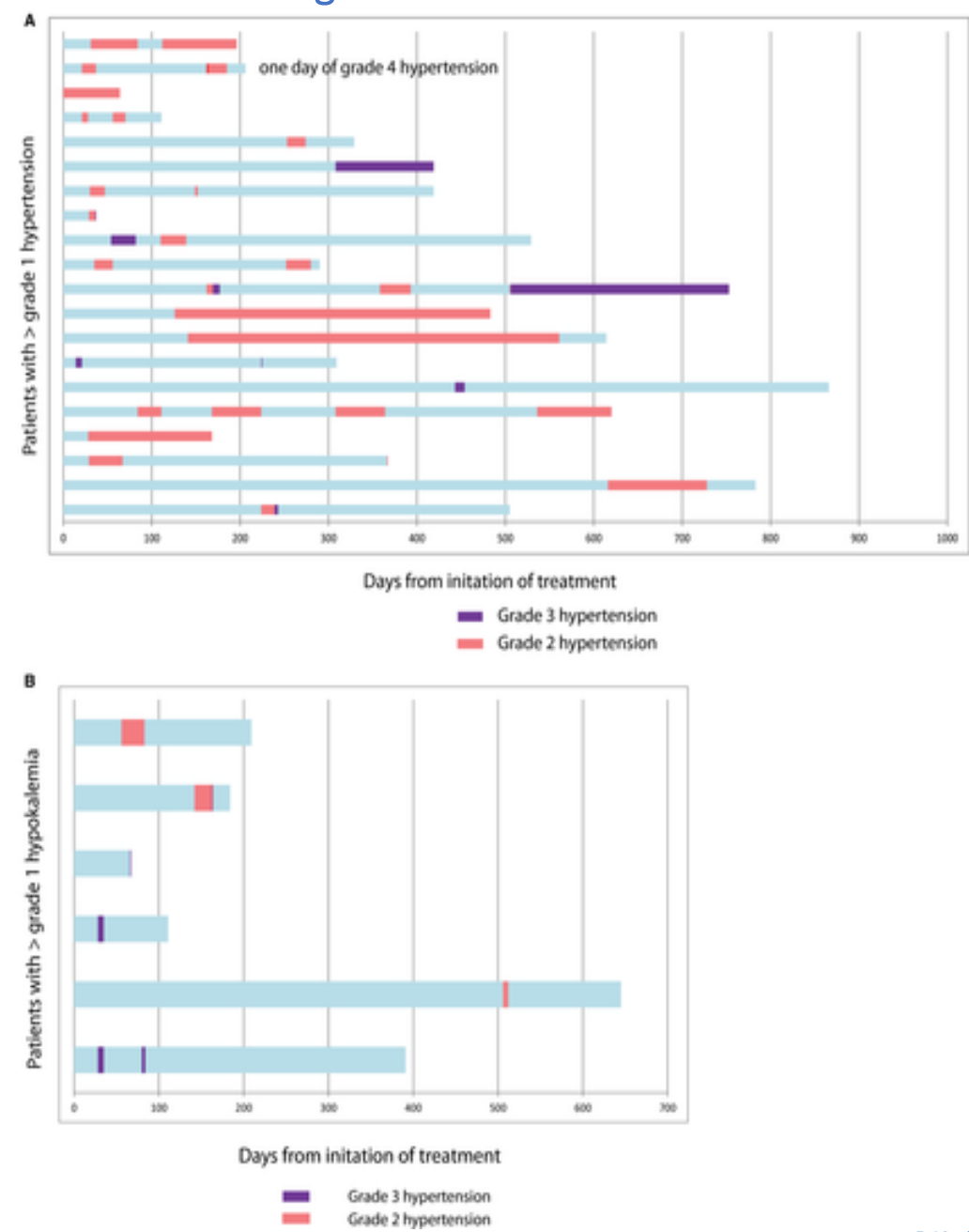
N = 58 (PCCTC: DFCI, MSK)

	Any grade	Grade 3-4	Latitude/Stampede (Grade 3-4) Pred 5mg qd
MT	66%	21%	
HTN	48%	15%	5-20%
Hypokalemia	26%	7%	1-11%
Edema	19%	0	0.3-1%

12% initiated prednisone for MT (4 hypokalemia, 3 HTN) not managed by anti-hypertensives or potassium supplements  
57% initiated anti-hypertensives, 19% potassium supplements

Conclusion: Abiraterone without steroids is feasible but requires close monitoring and algorithms to treat hypertension and hypokalemia when they arise – grade 1-2 very common and grade 3-4 – in 15-20%

A phase 2 trial of abiraterone acetate without glucocorticoids for men with metastatic castration-resistant prostate cancer



# Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer

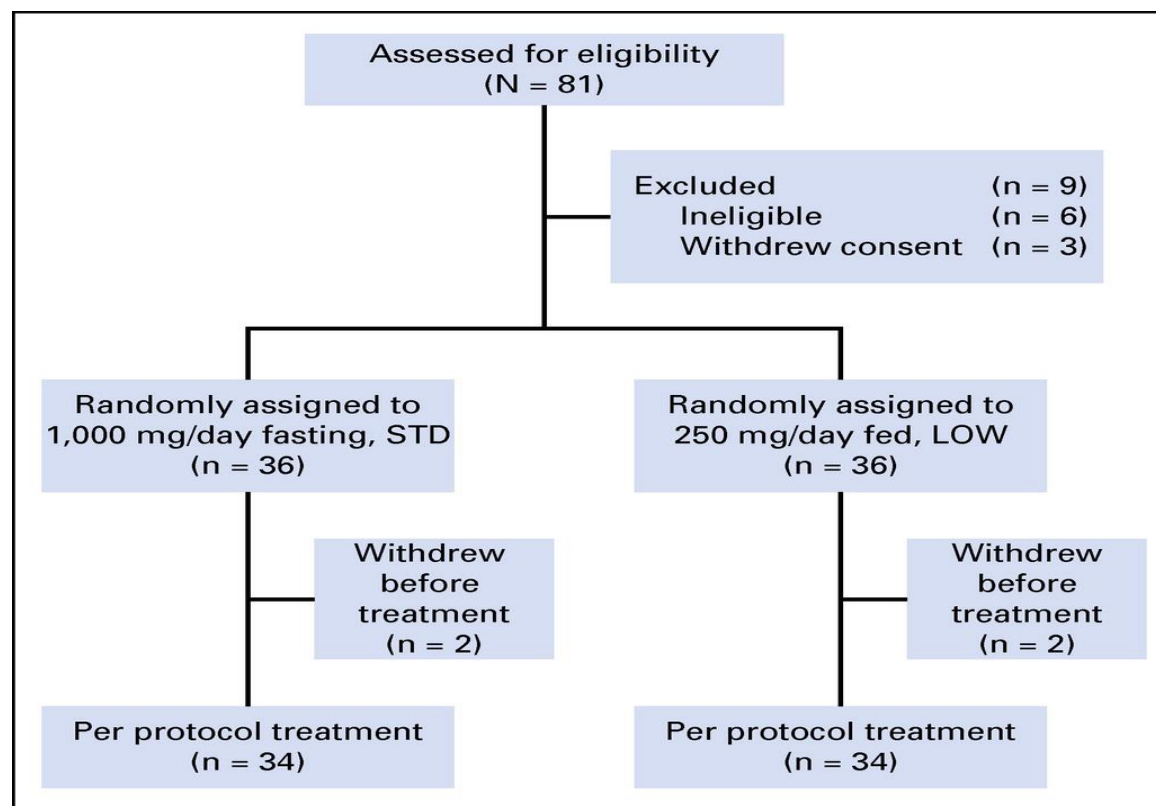
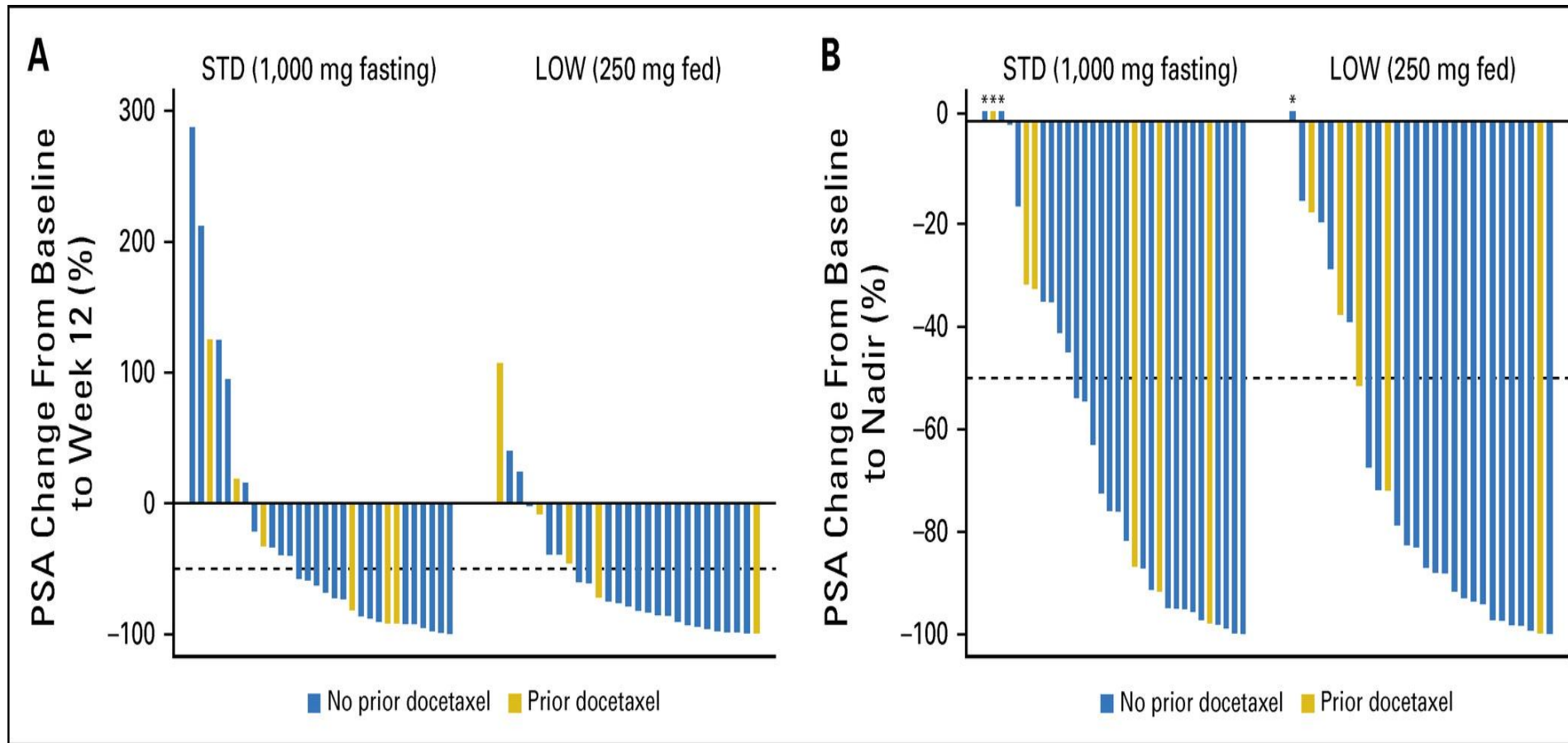


Fig 1. CONSORT diagram. LOW, 250 mg abiraterone acetate with a low-fat meal; STD, standard dose of 1,000 mg abiraterone acetate fasting.



*Fig2. Decrease in prostate-specific antigen (PSA) while receiving treatment. Waterfall plot showing percent reduction in PSA at (A) landmark 12-week time point and (B) maximum nadir. Patients whose best PSA response was progression are denoted with (\*). LOW, 250 mg abiraterone acetate with a low-fat meal; STD, 1,000 mg abiraterone acetate fasting*

Conclusion: While 1000mg should be considered the standard dose established with rigorous phase 1/2/3 trials, low dose with with food can be considered if circumstances support consideration (cost, patient preference). Close monitoring for efficacy over time is recommended.

# Conclusions

- No validated biomarkers to select therapy in first-line mCRCP after ADT + docetaxel or AR-axis therapy in HSPCa
- Clinical parameters of aggressive disease (short response to HSPCa therapy, high tumor burden, rapid pace of progression, visceral mets, poor genomics (p53, RB, myc) consider chemotherapy over other RX
- Favorable response to initial therapy many options: AR-axis Rx, Sip-T, Chemotherapy
- Genomically characterize tumor early in mCRPC when possible
- Abiraterone without steroids not recommended for routine use but can be considered with close monitoring and algorithms to treat HTN and hypokalemia
- Low dose Abiraterone with food can be considered in special circumstances with close monitoring for efficacy

# Basel – Silke, Aurelius, Secretariat

## Thank you for the memories!

