MAYO CLINIC
Cancer Center

Novel Hormonal Therapies for Prostate Cancer

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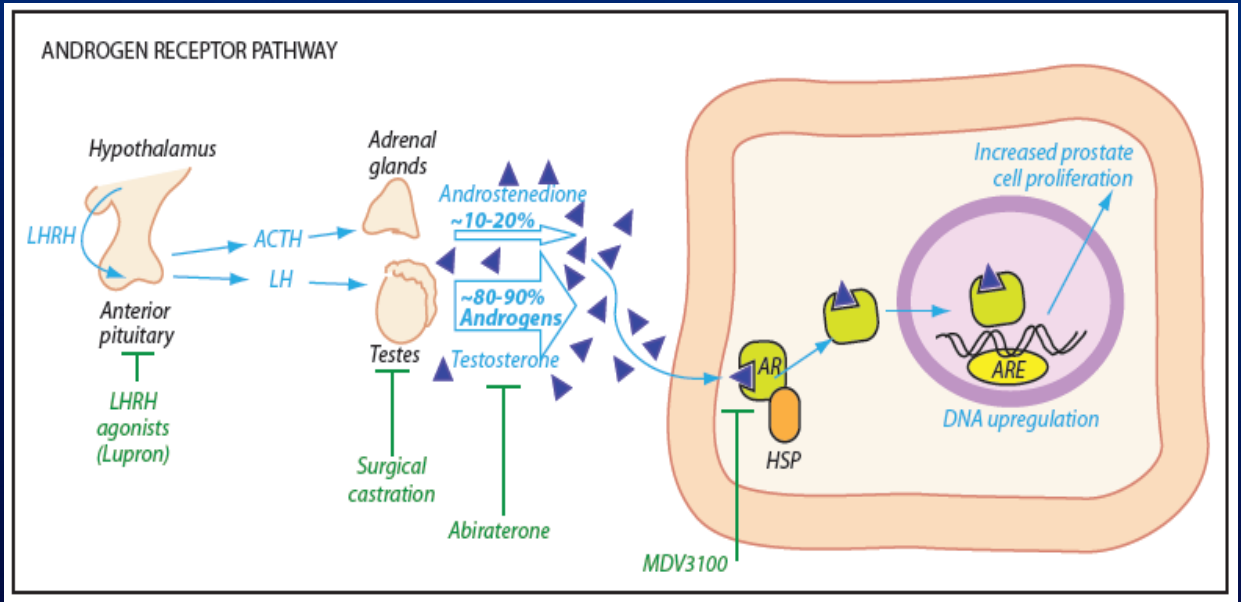
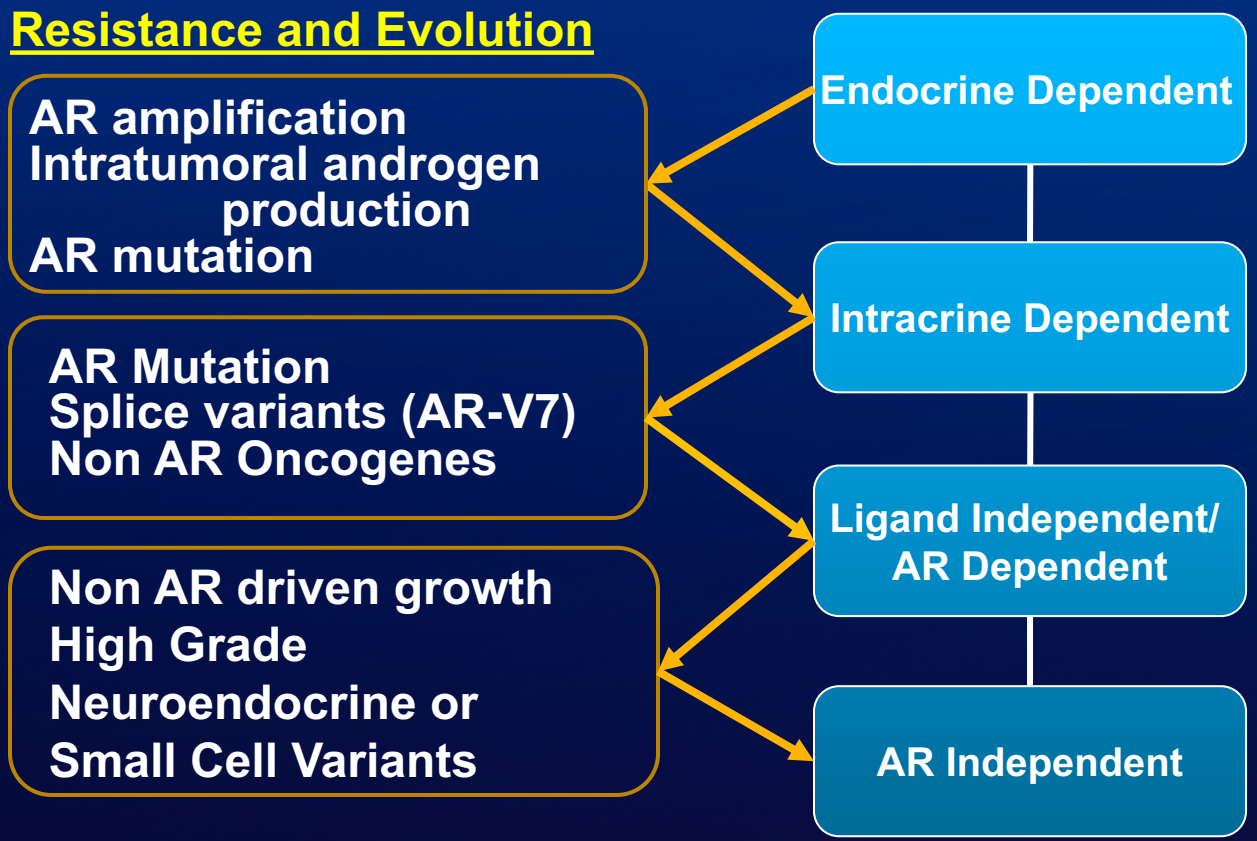
AR Pathway



Bryce AH, Ryan CJ. Clinical Pharmacology and Therapeutics 2011 (91): 101-108.

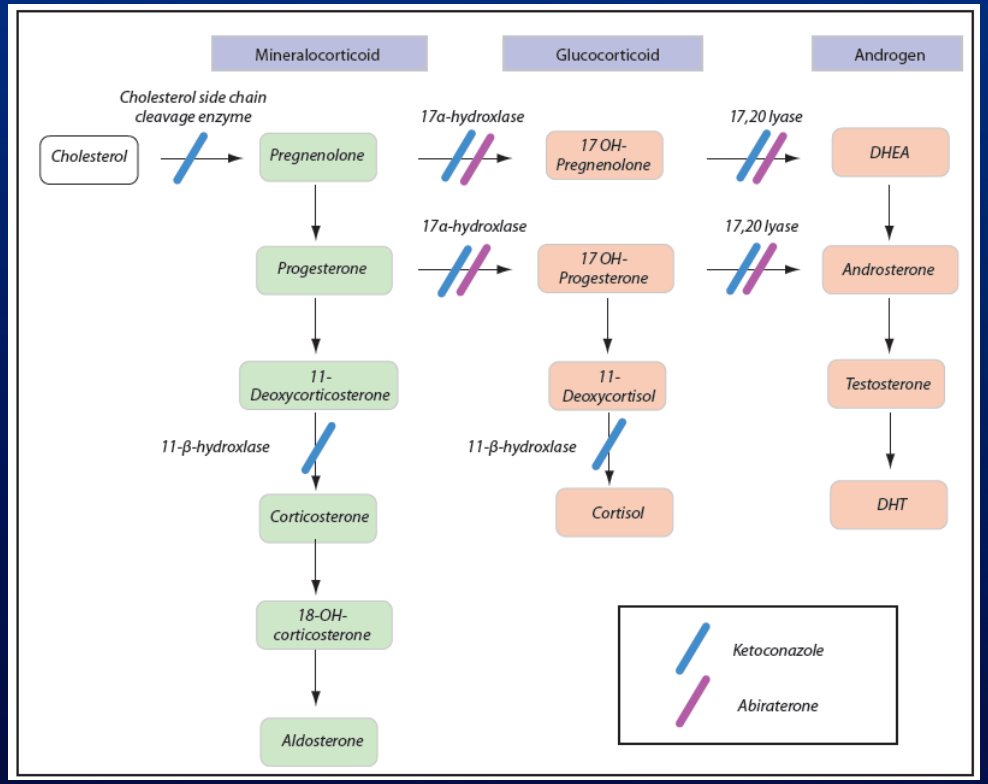
Progression of Metastatic PC



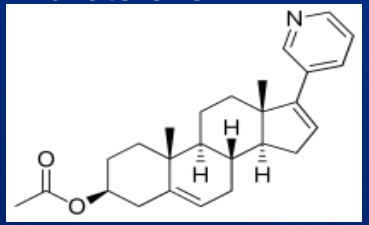
Hormone Therapy 2017
An Array of Options

- Cyp17A1 inhibitors
  - Abiraterone
  - Orterenol (Tak-700)
  - VT-464
- AR LBD inhibitors
  - Enzalutamide
  - Apalutamide (ARN509)
  - Darolutamide (ODM-201)
- AR NTD inhibitors
  - EPI-506
- BET inhibitors
  - GS-5829

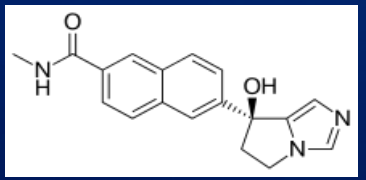
CYP17



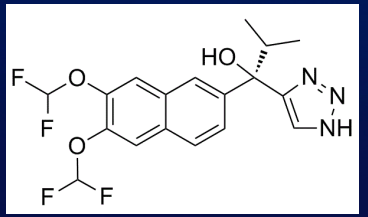
Abiraterone



Oreteronel



VT-464



Bryce AH. Clinical Pharmacology and Therapeutics. 2012; 91(1):101-8.

Orterenol (Tak 700)

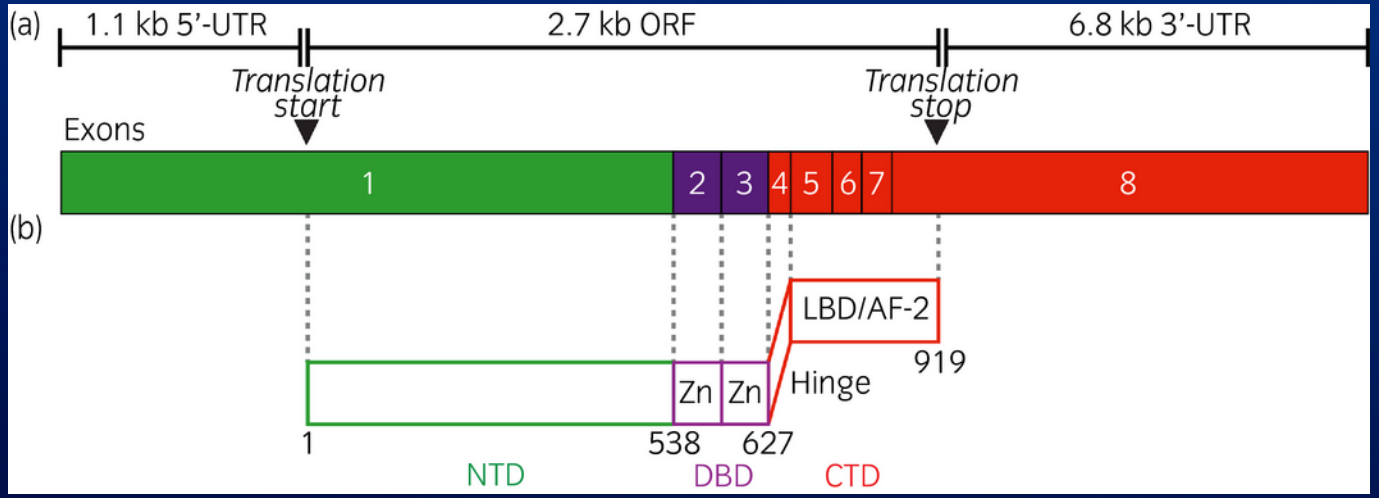
- Reversible non steroidal selective inhibitor of 17,20 lyase
- Failed to show OS benefit in CRPC (HR 0.90, 95% CI 0.70-1.10) despite PFS benefit, PSA progression benefit, and time to SRE benefit[1-3]
- Ongoing Studies
  - RTOG 1115- High risk localized disease, RT and CAB +/- orteronel
    - Anticipated completion 2020
  - SWOG 1216- mCSPC, Orteronel + ADT vs CAB
    - Anticipated completion 2020

[1]Saad F, et al. Lancet Oncol 2015;16:338-348. [2]Fizazi K, et al. JCO 2015;33:723-731. [3]Kang M, et al. Oncotarget 2017;8(35):59690-59697

VT-464

- Abiraterone Acetate requires concomitant Prednisone due to inhibition of 17α hydroxylase
- VT-464 has dual activity
  - 10 fold selectivity for Cyp17 lyase versus hydroxylase (no prednisone needed)
  - AR LBD antagonist, both wild type and mutant
  - Therefore potentially active post Abi or Enza
- Ongoing Phase I/II study in mCRPC post abi or enza

Androgen Receptor



Bryce, AH at al. International Journal of Urology Volume 23, Issue 8, pages 646-653, 3 JUN 2016 DOI: 10.1111/iju.13134

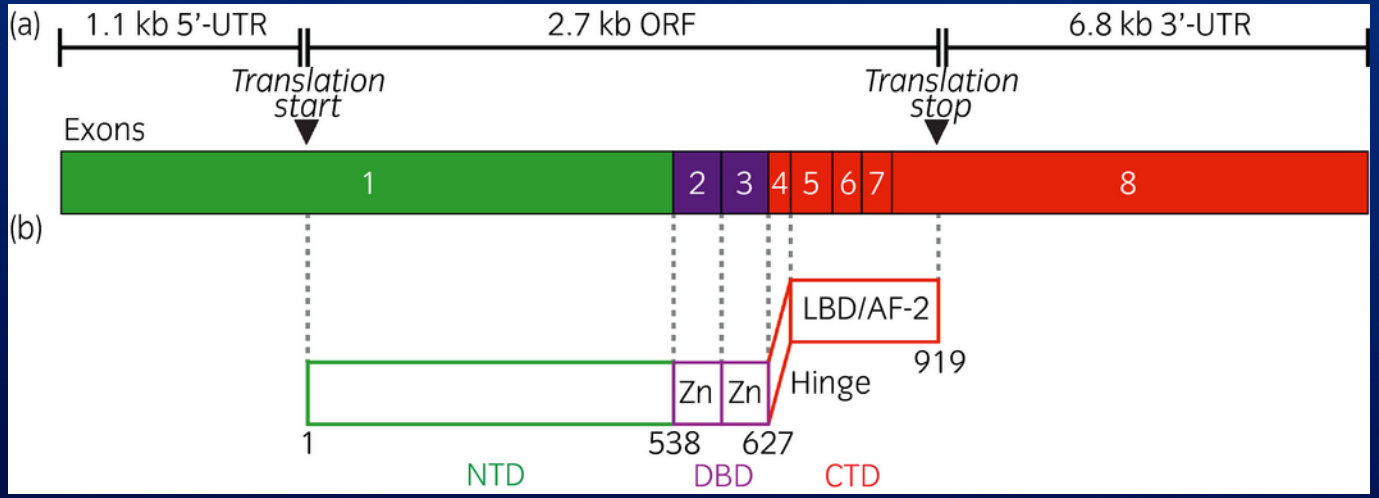
Apalutamide (ARN-509)

- Non Steroidal Anti androgen
  - AR antagonism 5-10x > bicalutamide
  - Less CNS penetration than Enzalutamide
    - Potential for less CNS toxicity
- NDA submitted based on the Spartan trial- M0, data not yet out.
- Ongoing Studies
  - Atlas- High Risk localized disease, randomized Ph 3,
  - Titan- HSPC Ph 3 study, ADT +/- apalutamide
  - AFT 19- M0 high risk (PSADT <9mos), randomized Ph3, three arm study of Degarelix vs D + Apalutamide vs D + Ap + abiraterone

Darolutamide (ODM-201)

- Non Steroidal Anti androgen
  - Also less CNS penetration than Enzalutamide
    - Potential for less CNS toxicity
  - *In Vitro* activity against AR F876L mutant PC
- Studies
  - ARADES- mCRPC, Ph I/II, complete
  - ARAMIS- M0 high risk, Darolutamide vs placebo
  - ARASENS- mHSPC, Randomized Phase III, ADT + docetaxel +/- Darolutamide

AR-V7 in mCRPC



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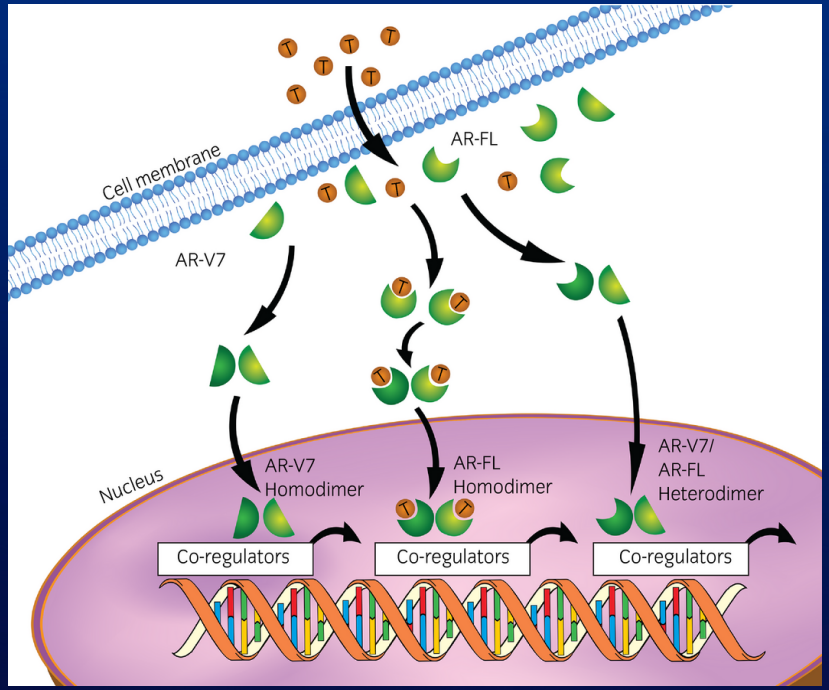
AR-V7 in mCRPC



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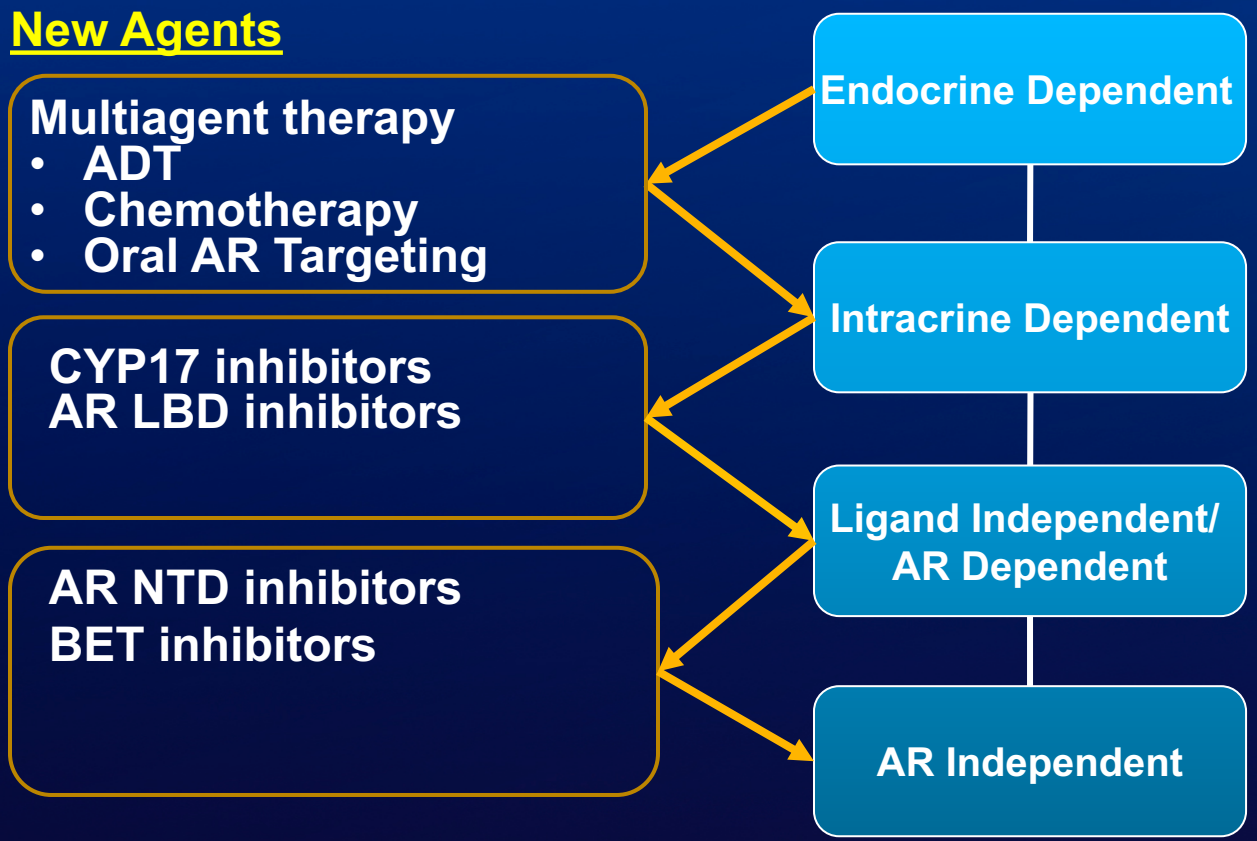
EPI 506

- Targets the NTD of the AR
  - Should be active against AR-V7 and other splice variants
- Phase I study in heavily pretreated patients
  - 4/21 patients had a PSA decline
  - 3 patients had SD >7 months

GS-5829

- Inhibitor of Bromodomain and Extraterminal proteins
- BRD 2,3,and 4 are essential regulators of AR and myc
  - Inhibition of BRD 2 prevents AR induced gene transcription
  - Cell line studies show activity verus ARV7
- Ph 1/2 study in refractory mCRPC ongoing

Next Generation AR Targeting



Thank You