

Prostate Cancer: State of a Rapidly Evolving Art

Advances in Hormonal Therapy for Advanced Prostate Cancer

Carmel Pezaro, Medical Oncologist

*Eastern Health Clinical School & Prostate Cancer Research Group
Monash University, Melbourne, Australia*

19 December 2015



Disclosure Slide

- I have received travel support and honoraria from:
 - Janssen
 - Sanofi
 - Astellas
 - Novartis
 - Pfizer

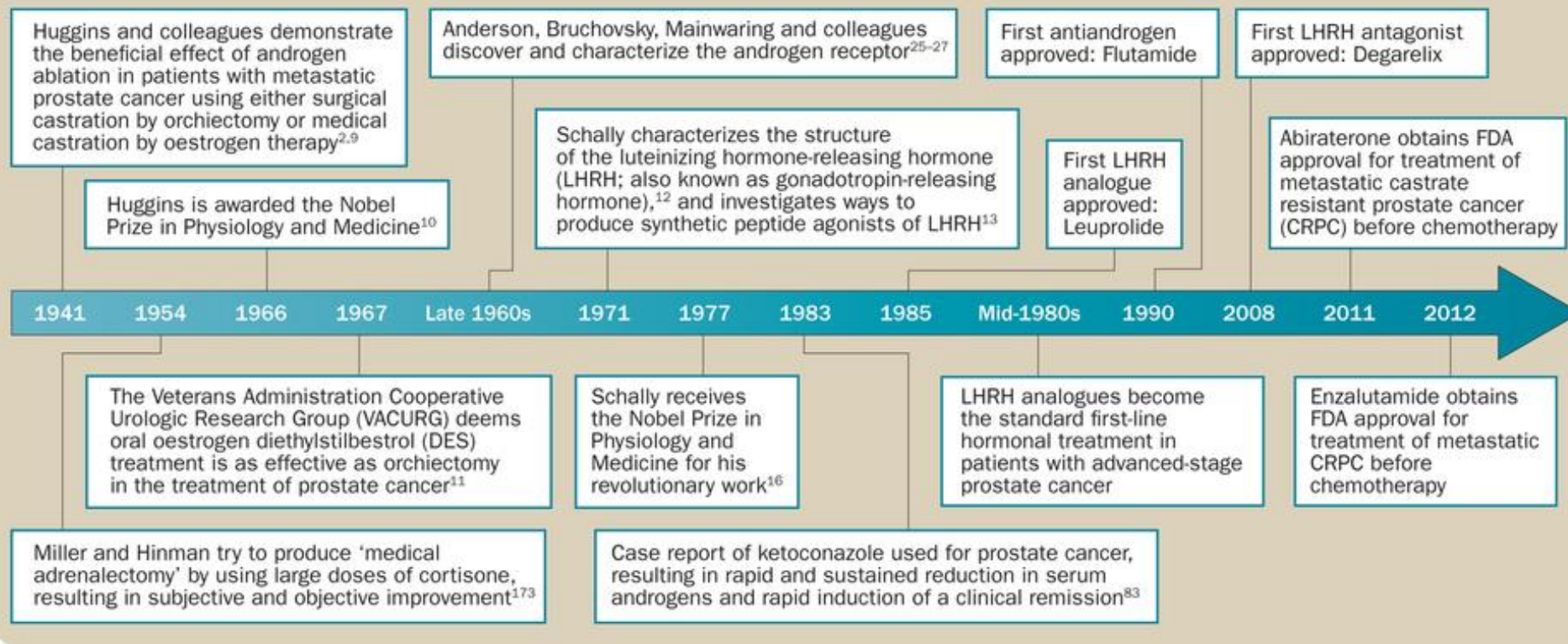


Key Points:

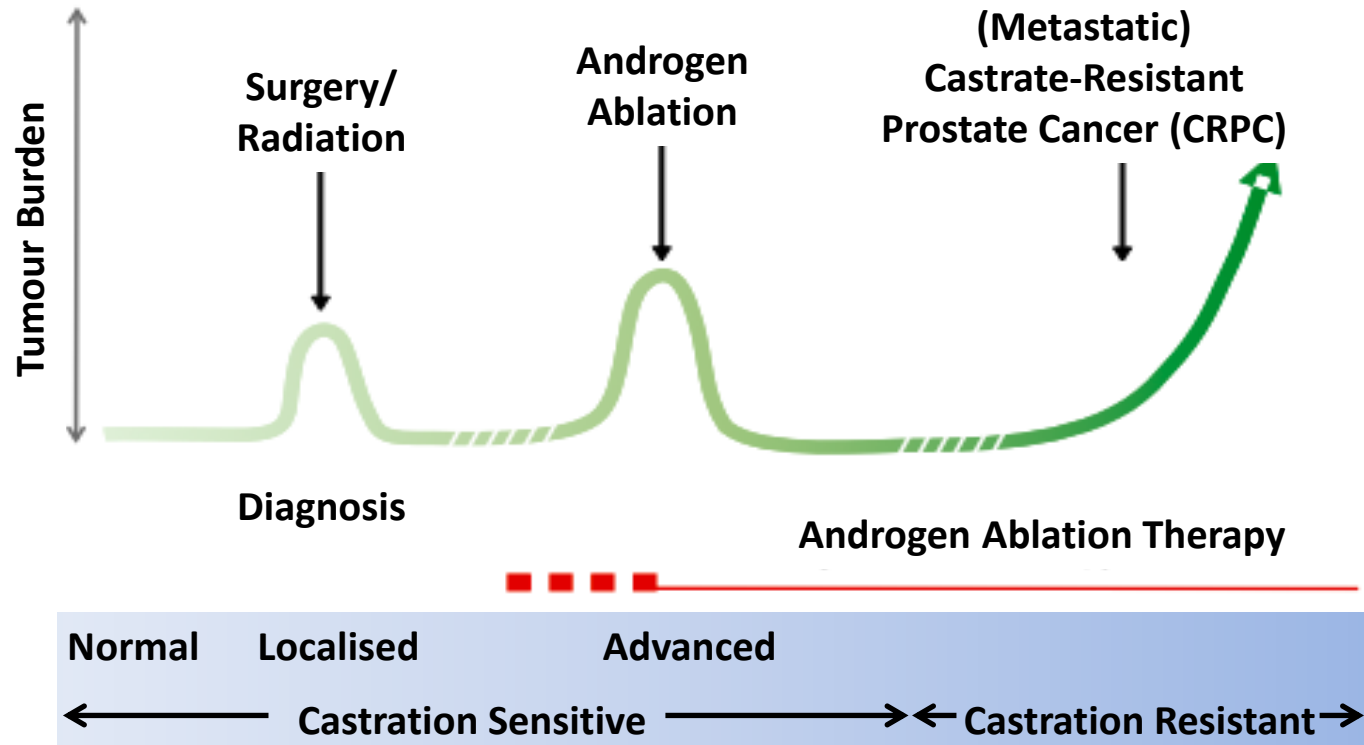
- Hormonal agents remain important therapeutic options in advanced prostate cancer (too).
- Hormonal signalling pathways are complex.
- One size does not (should not / will not) fit all.
- Further progress will come from learning how to better use agents we currently have – and those coming.

The Evolution of Hormonal Targeting

Timeline | Evolution of hormone strategies to treat prostate cancer



Currently We Face a Choice Paradox in CRPC



DOCETAXEL	DOCETAXEL
'Pre-chemotherapy'	'Post-chemotherapy'
Abiraterone acetate Enzalutamide Sipuleucel-T Trial therapies	Abiraterone acetate Enzalutamide Cabazitaxel Radium ²²³ Trial therapies

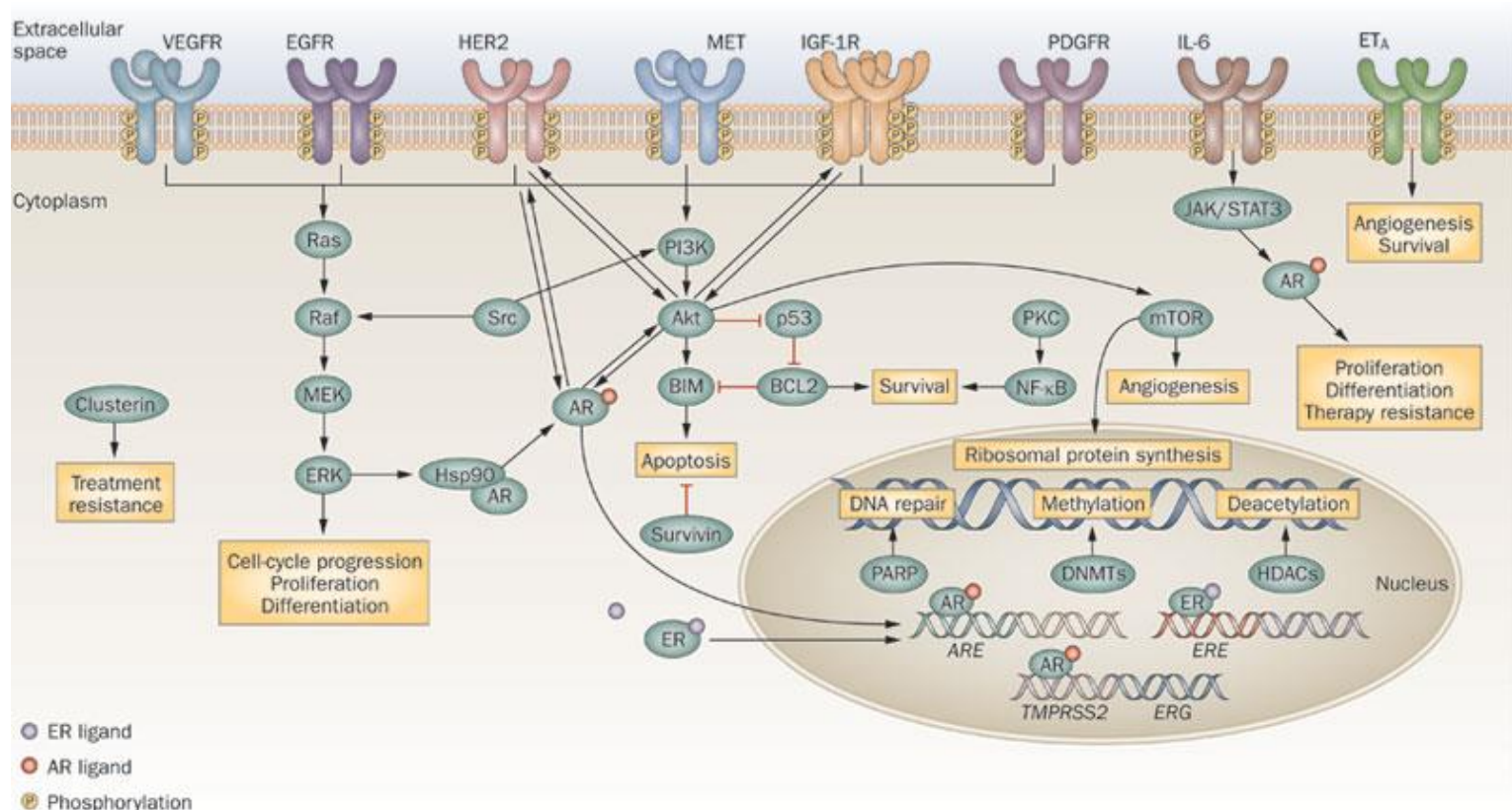


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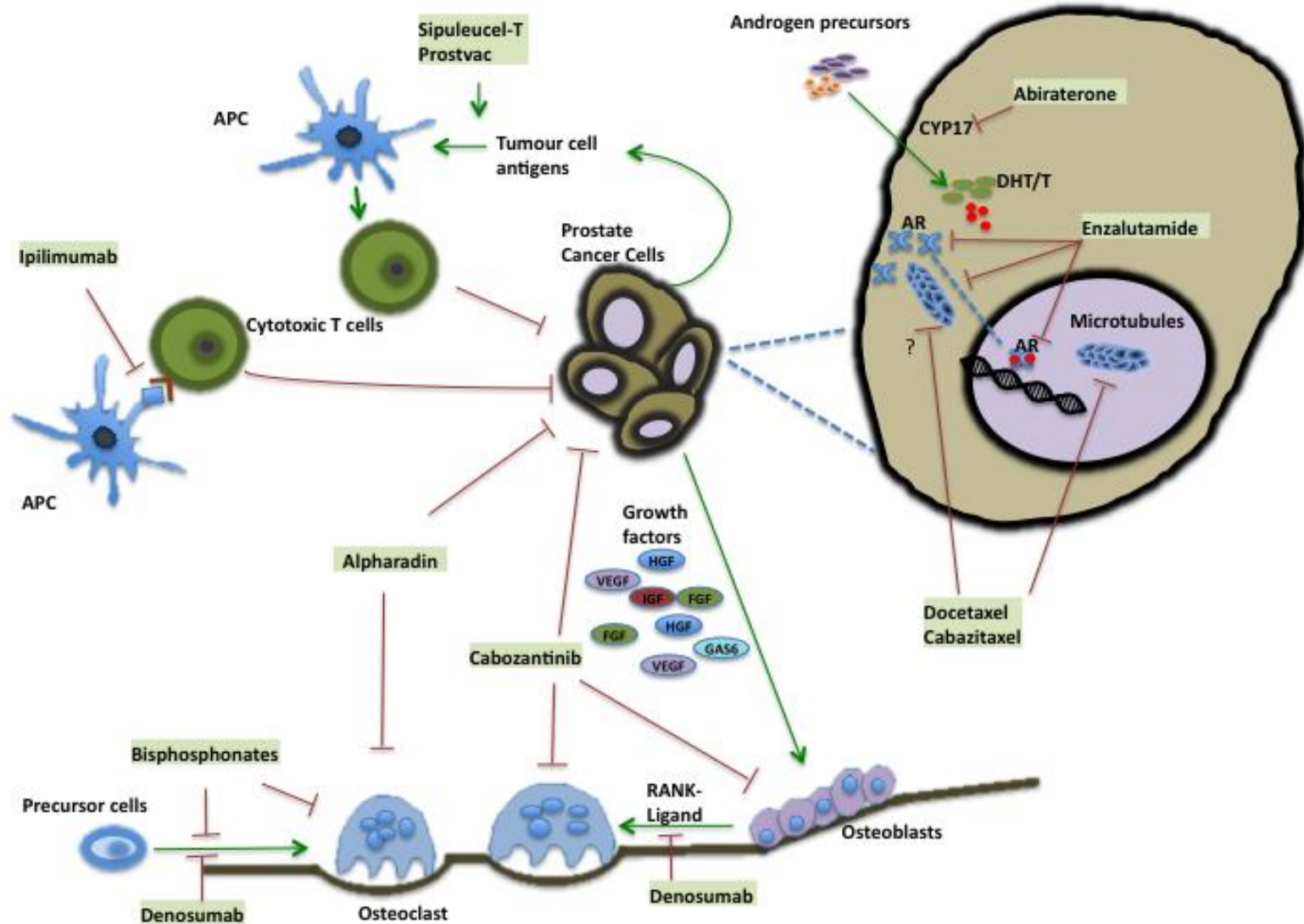
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Androgen Receptor (AR) in Prostate Cancer

- AR activated in cytoplasm, translocated to nucleus, binds and activates AR-target genes
- AR addiction is a hard habit to break

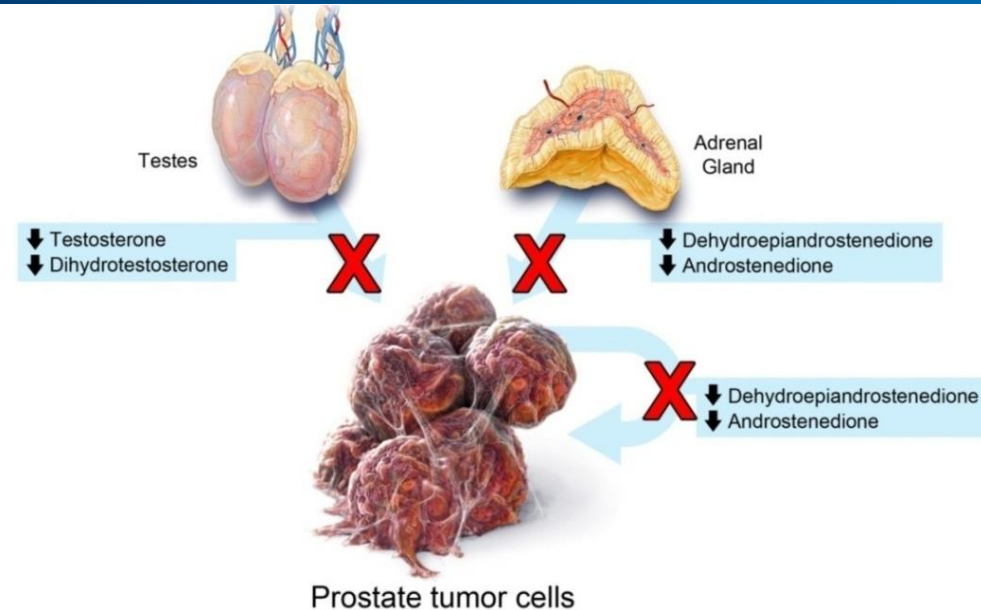


Hormonal Targets Remain Relevant in Advanced Prostate Cancer



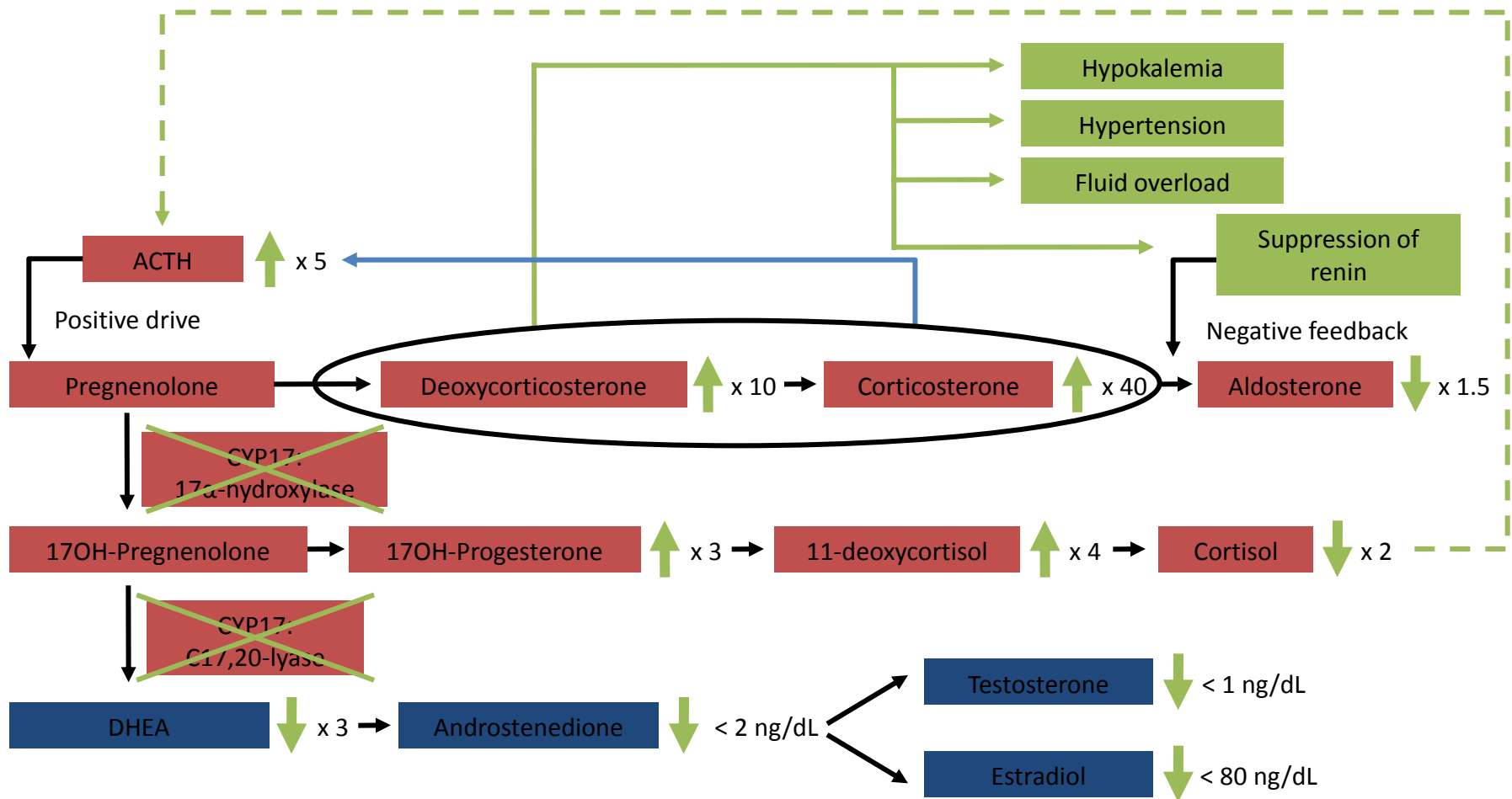
Abiraterone Acetate: Androgen Biosynthesis Inhibitor

- Androgens produced at 3 critical sites lead to tumor proliferation
- Abiraterone inhibits biosynthesis of androgens

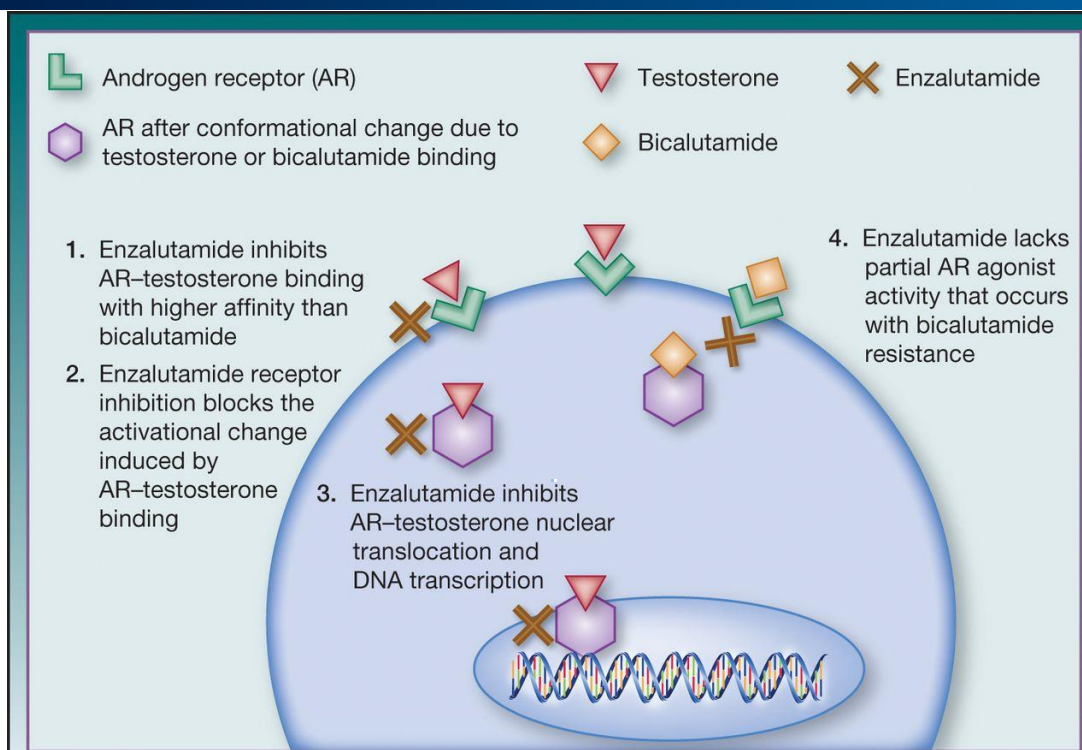


Study	N	Endpoints	Analyses
Post-chemotherapy <u>301</u>: Abiraterone/Pred vs. Placebo/Pred	1195	Overall survival	15.8 vs. 11.2m (HR 0.74, 95% CI 0.64 – 0.86) *final analysis
Pre-chemotherapy <u>302</u>: Abiraterone/Pred vs. Placebo/Pred	1088	Overall survival Radiographic PFS	34.7 vs. 30.3m (HR 0.8, 95% CI 0.69-0.34) **final analysis 16.5 vs. 8.3m (HR 0.53, 95% CI 0.45 – 0.62)

Abiraterone: Mechanism of Action + Toxicity



Enzalutamide: Second Generation Anti-Androgen



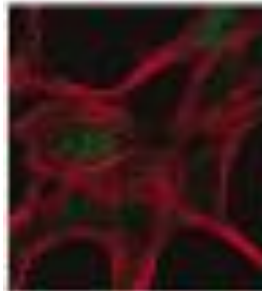
Study	N	Endpoints	Analyses
Post-chemo <u>AFFIRM</u>: Enzalutamide vs. Placebo	1199	Overall survival	18.4 vs. 13.6m (HR 0.63, 95% CI 0.53 – 0.75)
Pre-chemo <u>PREVAIL</u>: Enzalutamide vs. Placebo	1717	Overall survival rPFS	35.3 vs. 31.3m (HR 0.77, 95% CI 0.67-0.88) *Final analysis NR vs. 3.9m (HR 0.19, 95% CI 0.15 – 0.23)

Taxanes: The Original Novel Hormonal Therapy?

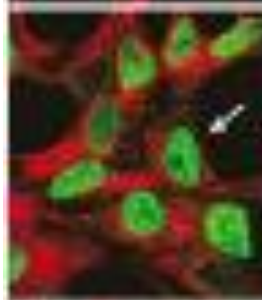
• *In vitro*:
Confocal
microscopy

Red= tubulin
Green= AR

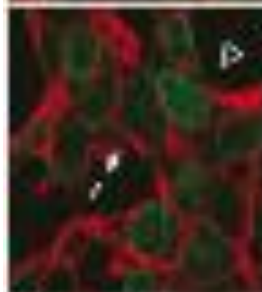
Arrowheads:
microtubule
bundles



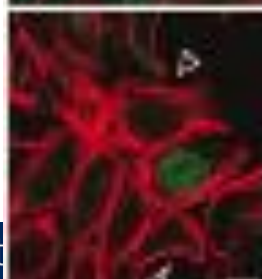
A: Control



**B: DHT
analogue**



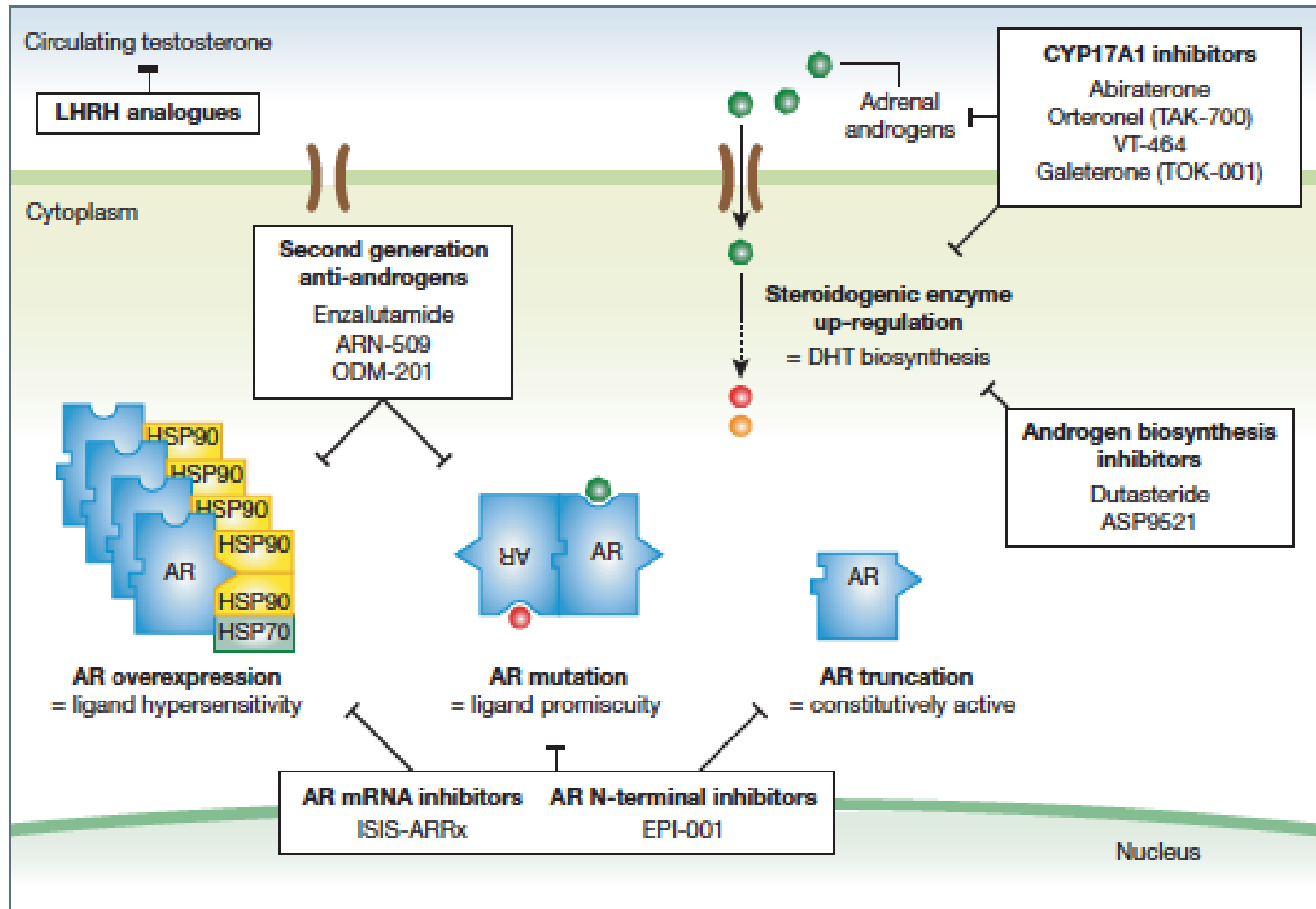
**C: Paclitaxel
+ DHT
analogue**



D: Paclitaxel

- AR in Circulating Tumour Cells:
 - 14 pts receiving taxanes.
 - 13/18 samples during 'clinical progression' showed NUCLEAR AR localisation.
 - 12/17 samples during 'response/stable disease' showed CYTOPLASMIC AR localisation.
 - Cytoplasmic AR localisation seen as early as 1-hour post taxane.

Additional AR-Targeting Agents in Development

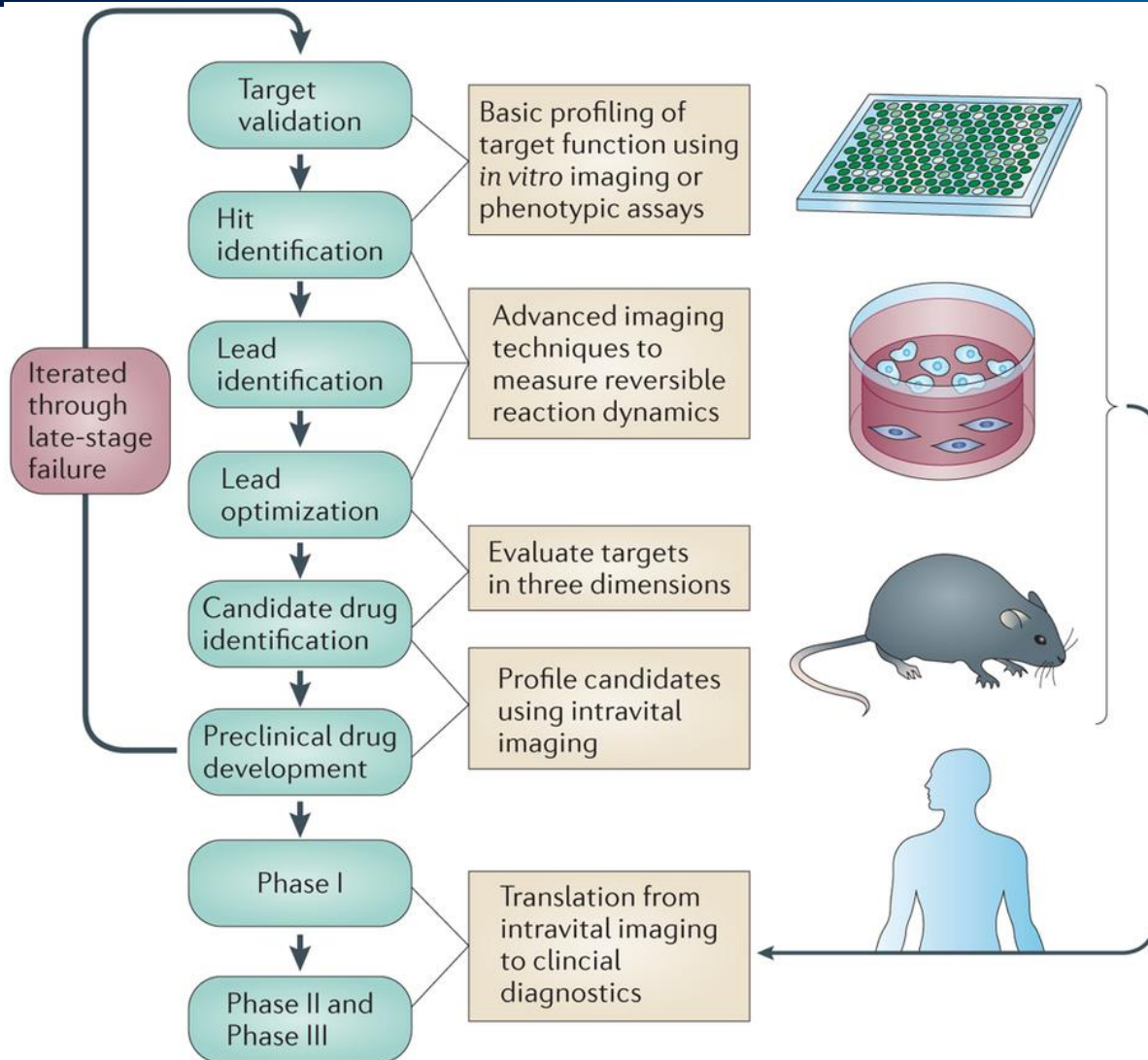




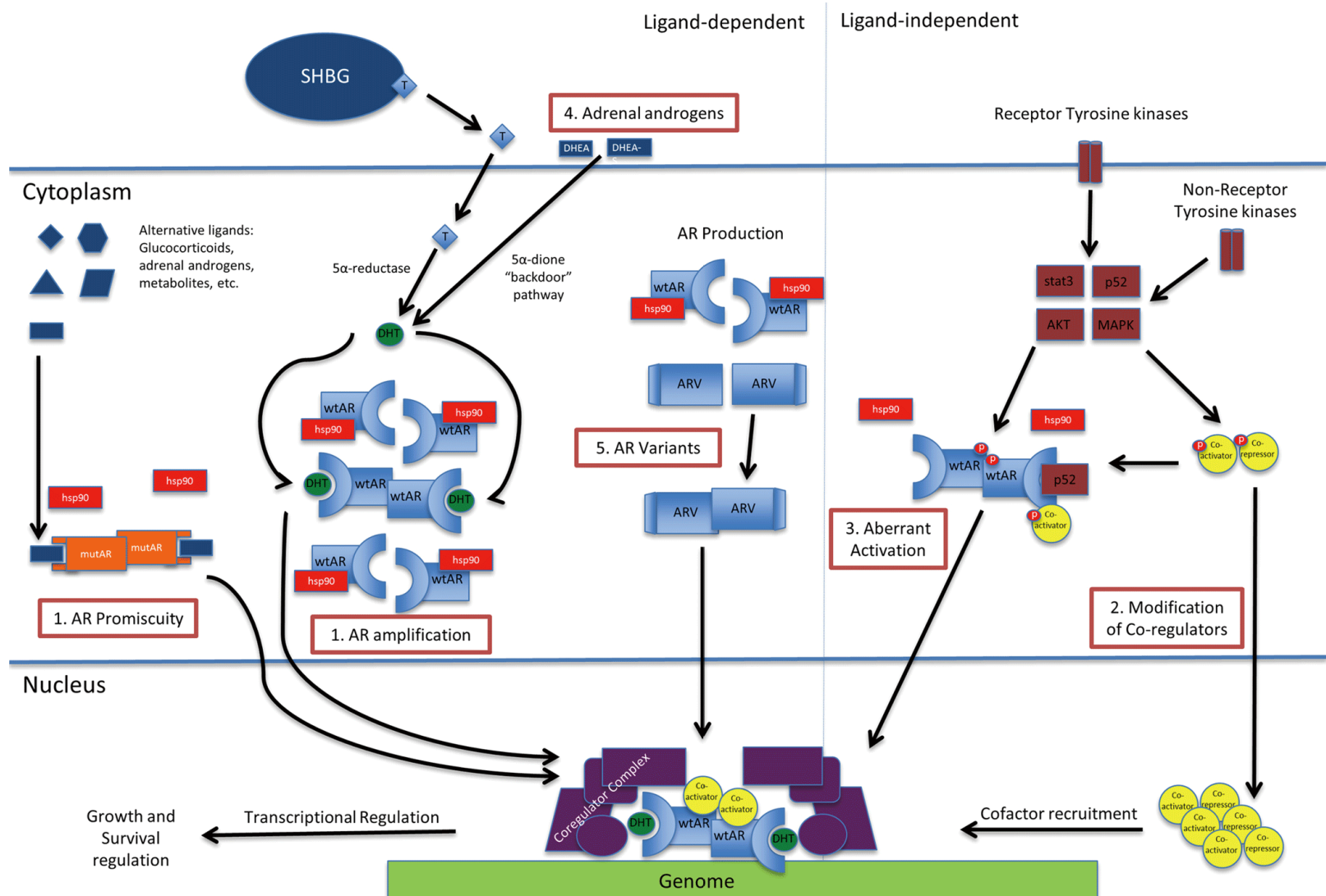
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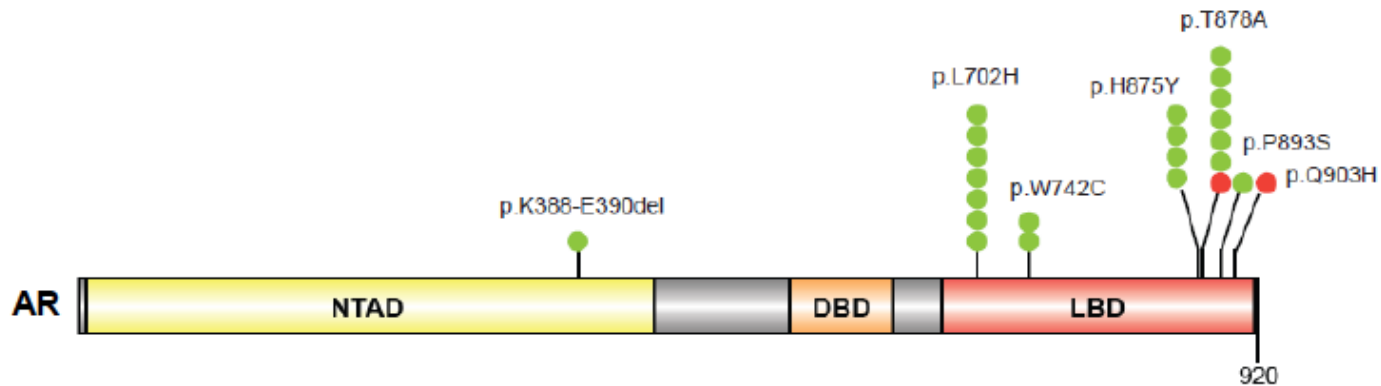
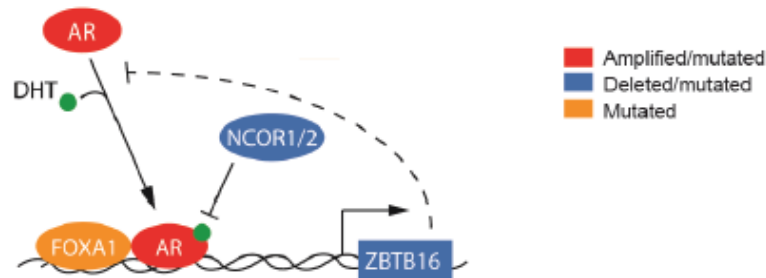
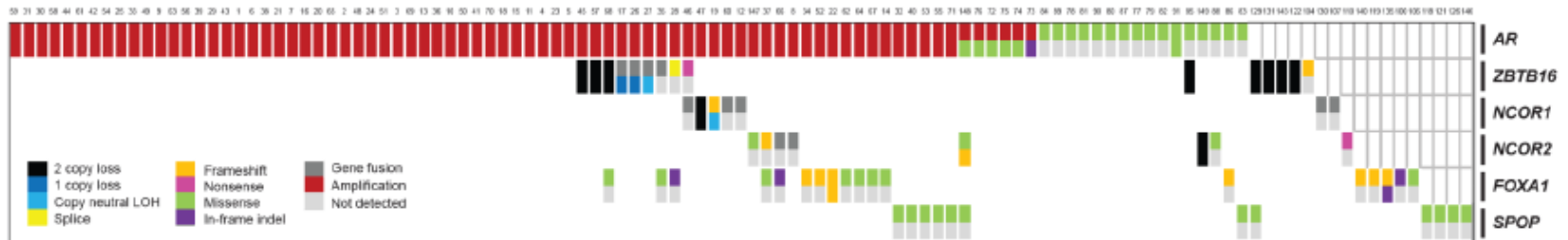
Increasingly Complex Models = Increased Variability of Response



Mechanisms of Castration Resistance



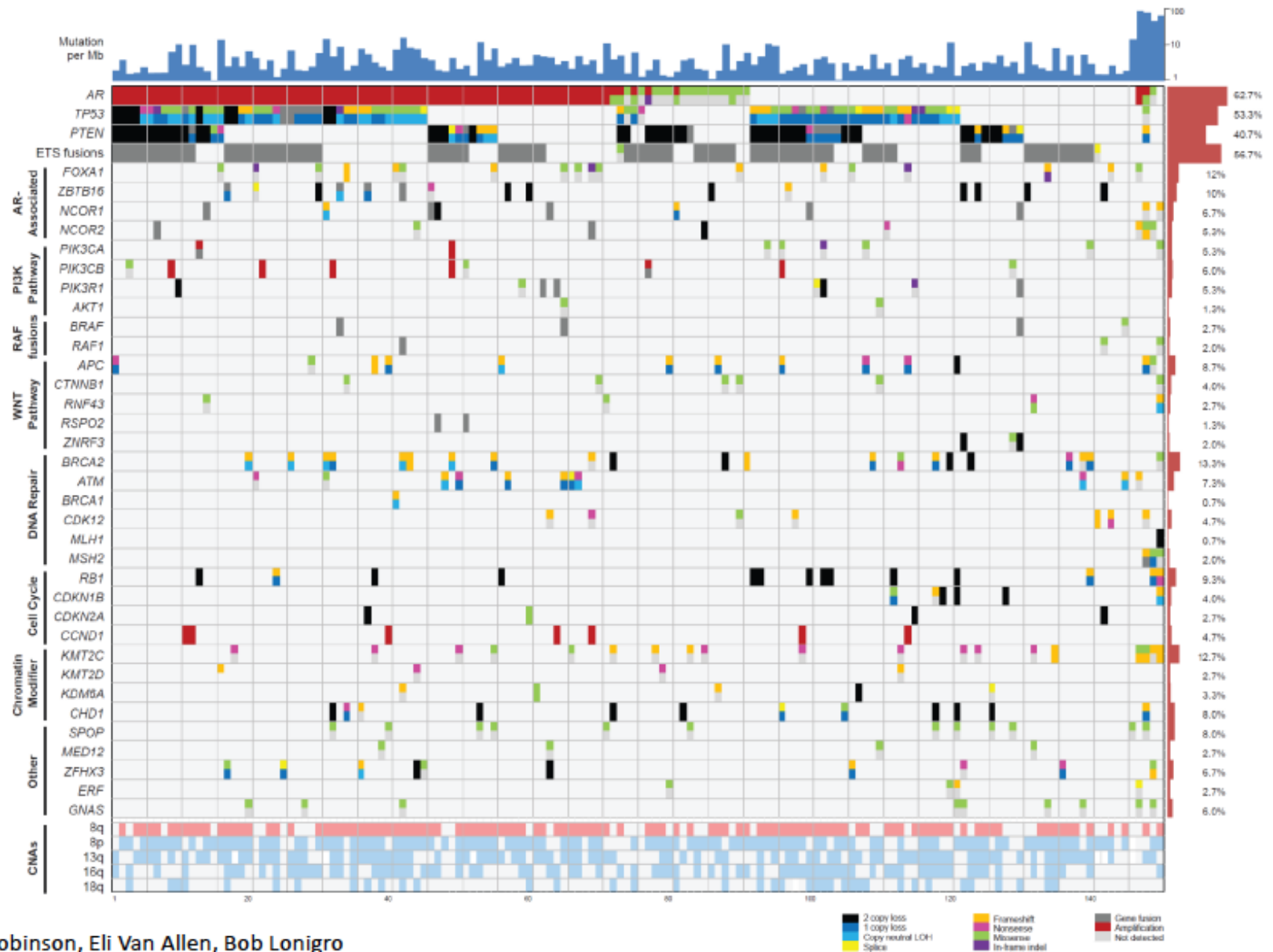
AR Pathway Aberrations Increased in CRPC



Non-synonymous mutations identified in AR

● MO_1040 harbors two mutations: p.T878A and p.Q903H

Genomic Landscape Reveals CRPC Complexity



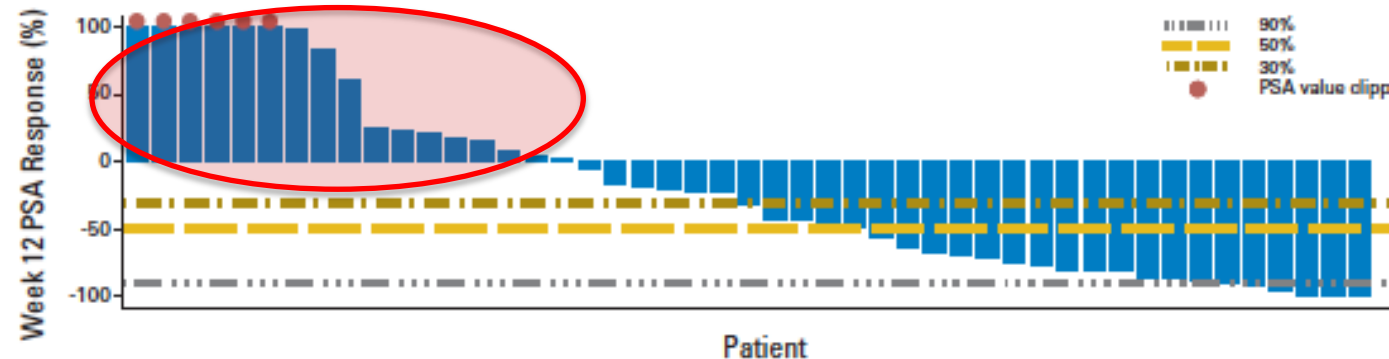


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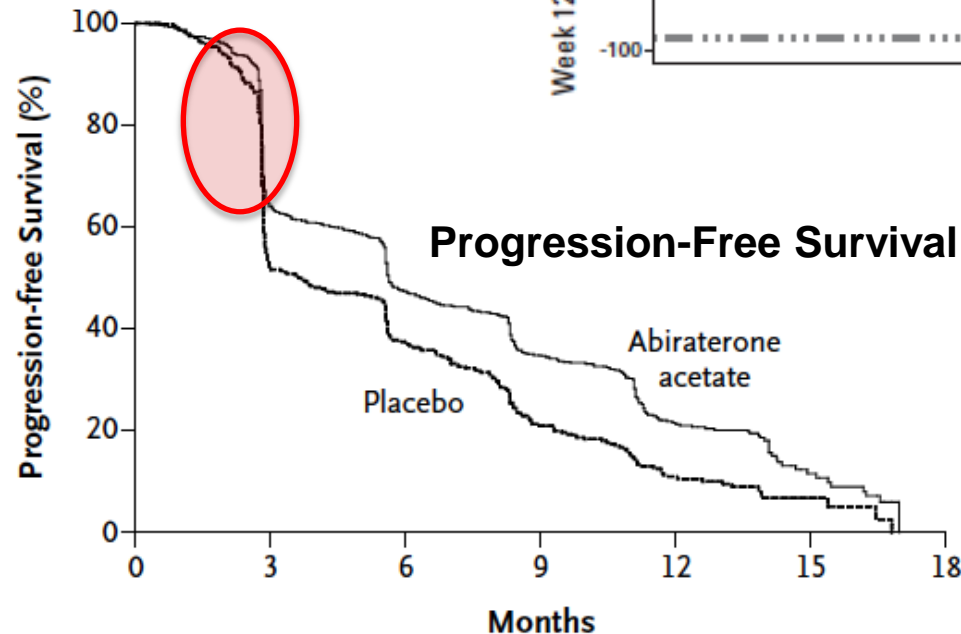
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Looking Beyond the Bottom Line in Clinical Trials

PSA Decline on Abiraterone Phase II Trial



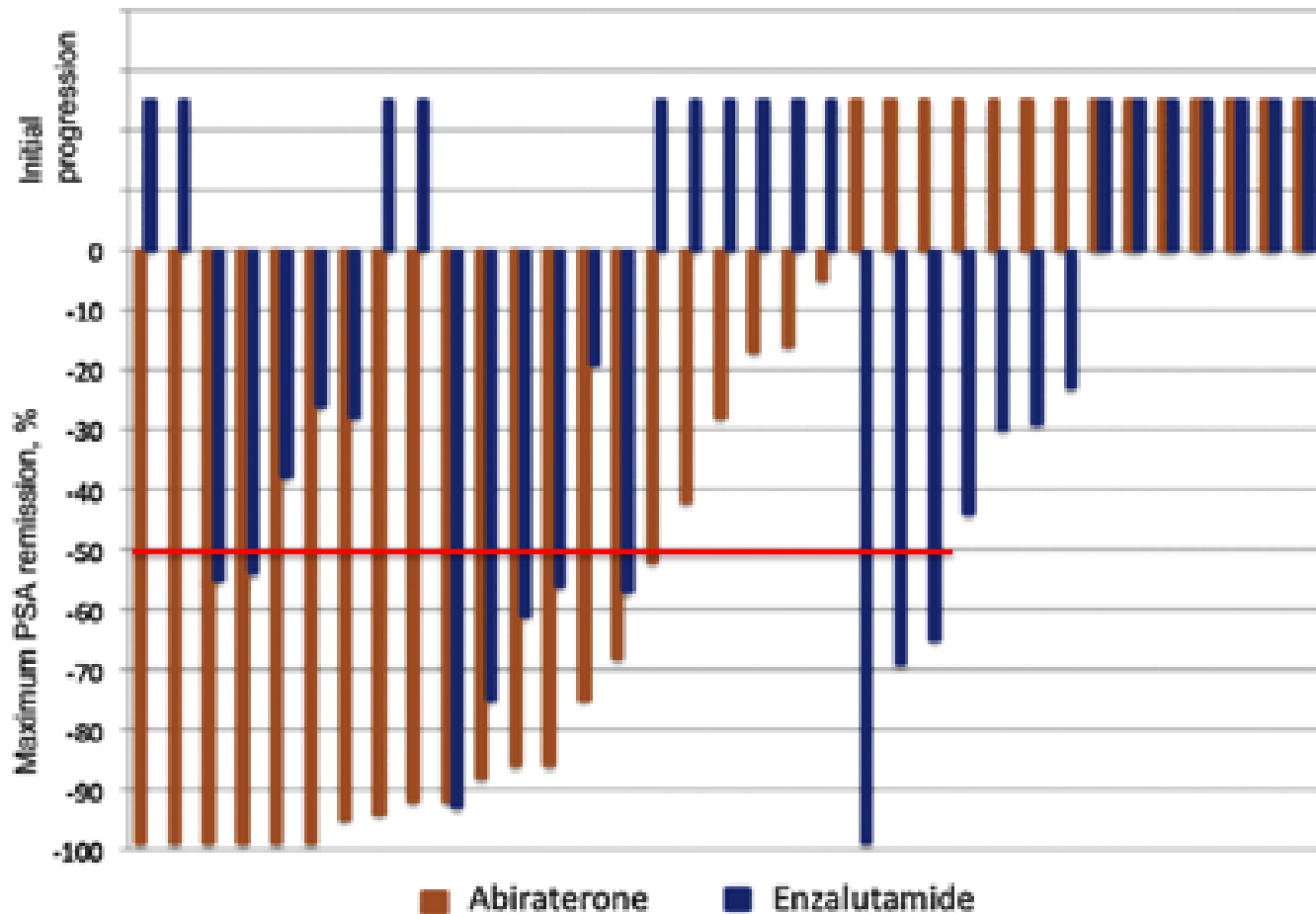
Progression-Free Survival on Abiraterone-301 Trial



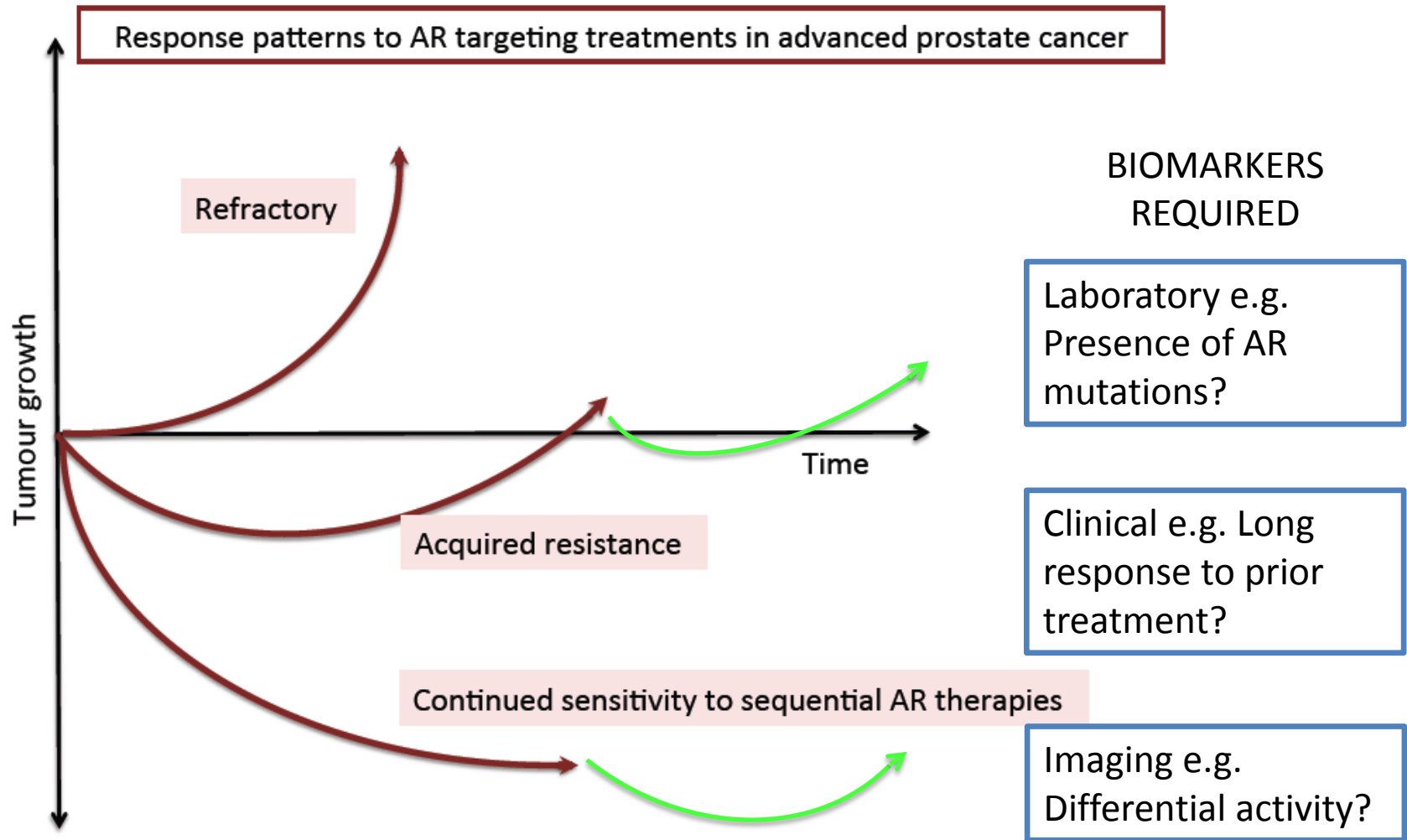
797	490	352	202	76	14	0
398	193	129	64	22	4	0

Sequencing Cohorts Reveal Further Heterogeneity

Case series: 35 patients Abi - Enza



How Do We Approach Individualised Treatment?





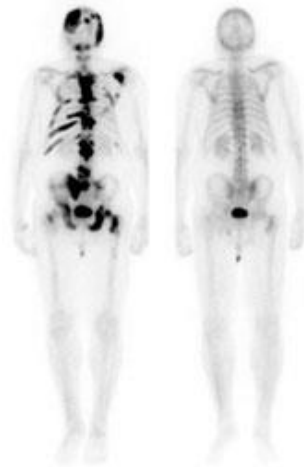
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State-of-the-Art Treatment Requires State-of-the-Art Assessments

- Out with old imaging!
 - Bone scan: ‘better than an x-ray’ = 3 monthly on-trial assessments??
 - CT/BS: progression focus
 - Unreliable

...Cabozantinib



- Bring in biomarkers!
 - PSA \neq survival surrogate
 - PFS unreliable (TAK-700)
 - Hb, ALP, albumin slow and late
 - CTC / cfDNA easily accessible, promising (but may still hide heterogeneity)
 - Need validating across trials / populations / platforms

- Newer technologies: response + progression data:
 - Diffusion-weighted MRI
 - PSMA/Na/F/CI PET

Where Are Current Hormonal Agents Moving?

- Combinations:
 - Upfront
 - Addition on progression
- Earlier in disease:
 - M0 CRPC (if this really exists)
 - Hormone-sensitive
 - Biochemical recurrence
 - Neo-adjuvant



Combination Studies Deserve Enthusiasm + Caution

~50 Abi-combo trials on Clinical Trials, ~35 Enza-combinations

Docetaxel / Cabazitaxel

Enzalutamide / ARN509 (JNJ56021927)

Radium-223

Ipilimumab

HSP90 inhibitors

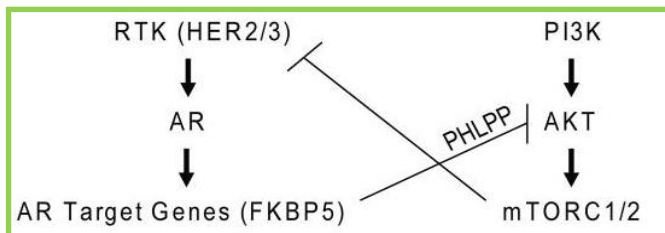
VEGFR inhibitors

PSA-TRICOM

PI3K / mTOR / AKT inhibitors

...

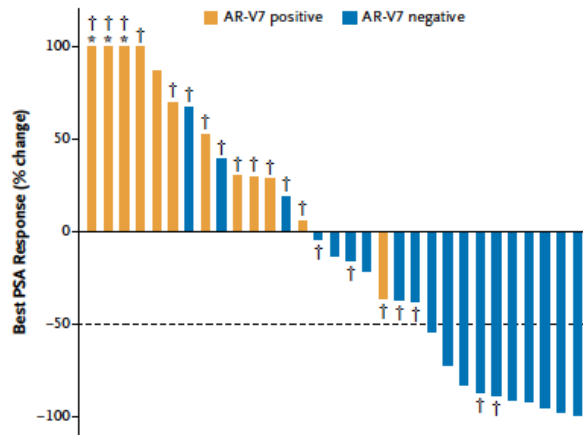
Reciprocal regulation in PTEN-deficient prostate cancer



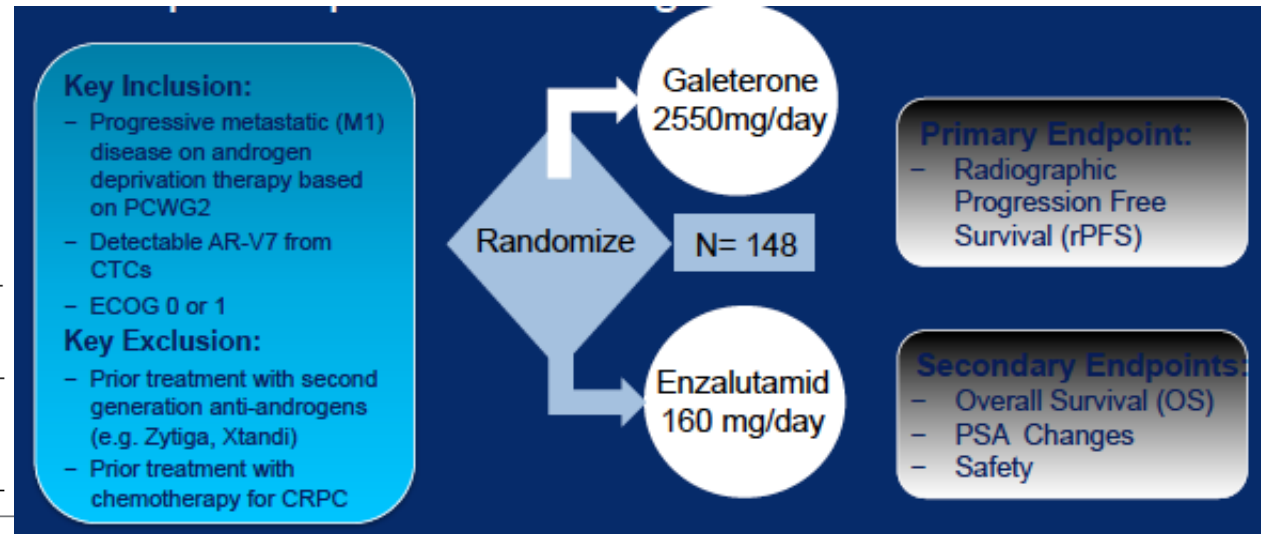
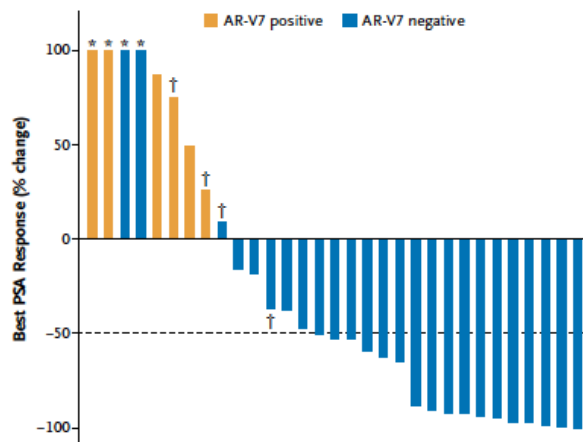
Liquid Biomarkers May Predict Efficacy of AR Targeting

- PSA response by ARv7 status → ARMOR3-SV Trial

A Enzalutamide-Treated Patients



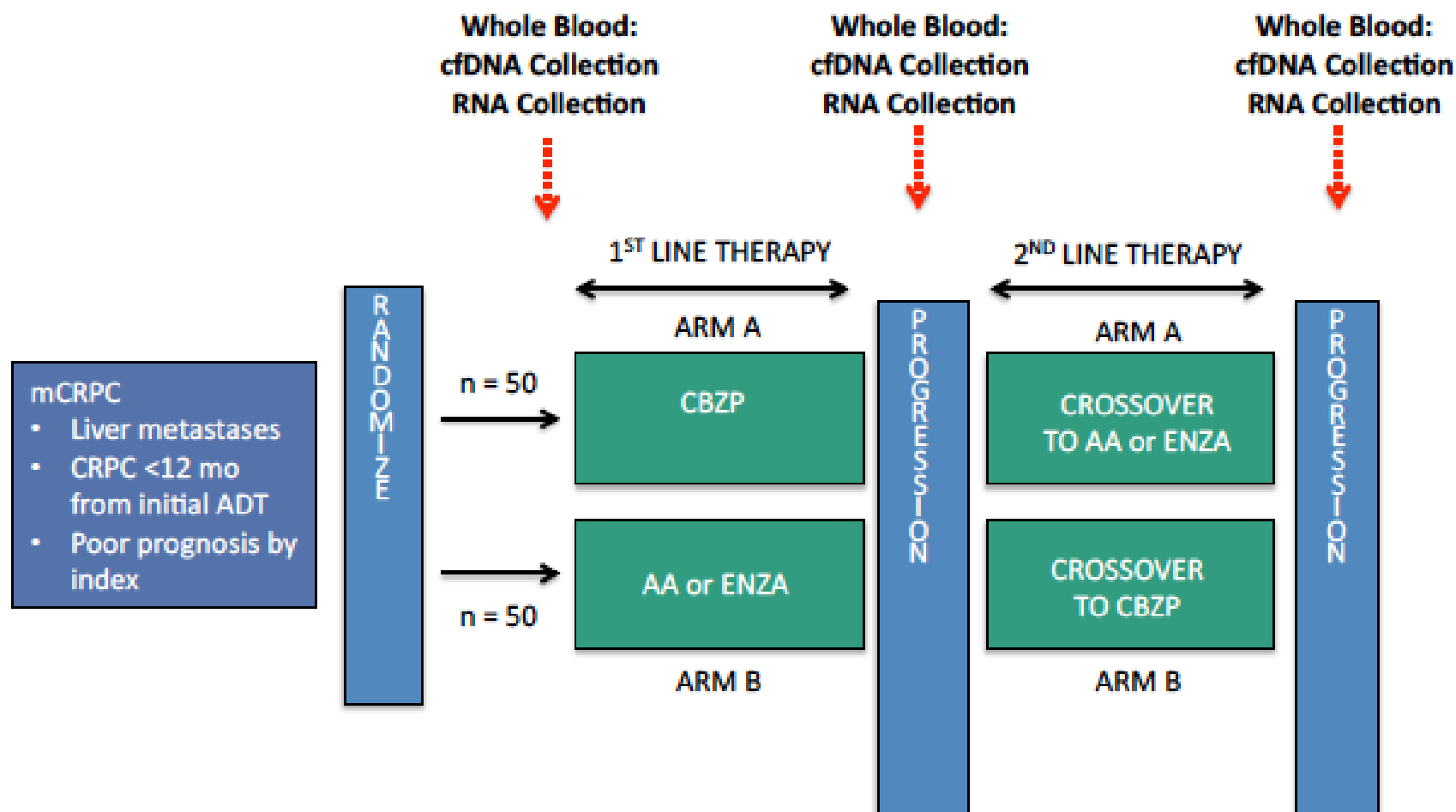
B Abiraterone-Treated Patients



- AR amplification:
 - Associated with treatment resistance in abiraterone and enzalutamide cohorts

Biomarker-Embedded Research

OZM-054: A phase 2, randomized, multicenter study



CBZP: cabazitaxel; ENZA: enzalutamide

ClinicalTrials.gov: NCT02254785; PI: K. Chi

Should We Challenge the Basic Premise of Castration?

- Enzalutamide monotherapy:
 - 62 of 67 men in phase II trial has PSA decline $\geq 80\%$ at week 25
 - Most common adverse events G1-2 gynaecomastia, fatigue
 - LH and testosterone increased from baseline
- Bipolar androgen therapy:
 - Castration with intermittent supraphysiologic testosterone
 - PSA response in 7 of 14 evaluable patients
 - ?Improved sensitivity to subsequent ADT

Conclusions

- Hormonal treatment options for men with advanced prostate cancer have markedly improved in the past decade.
- It is extremely unlikely that there is an optimal 'one size fits all' sequence.
- We must prioritise initiatives that enable treatment prediction and earlier recognition of progression.
- Further innovation will result from identifying patient subtypes for current and new hormonal treatments AND from improved methods of assessing treatment response.





THANK YOU

