"ESTRATEGIAS PARA ABORDAR LA RESISTENCIA A TERAPIA ENDOCRINA EN CÁNCER DE PRÓSTATA"

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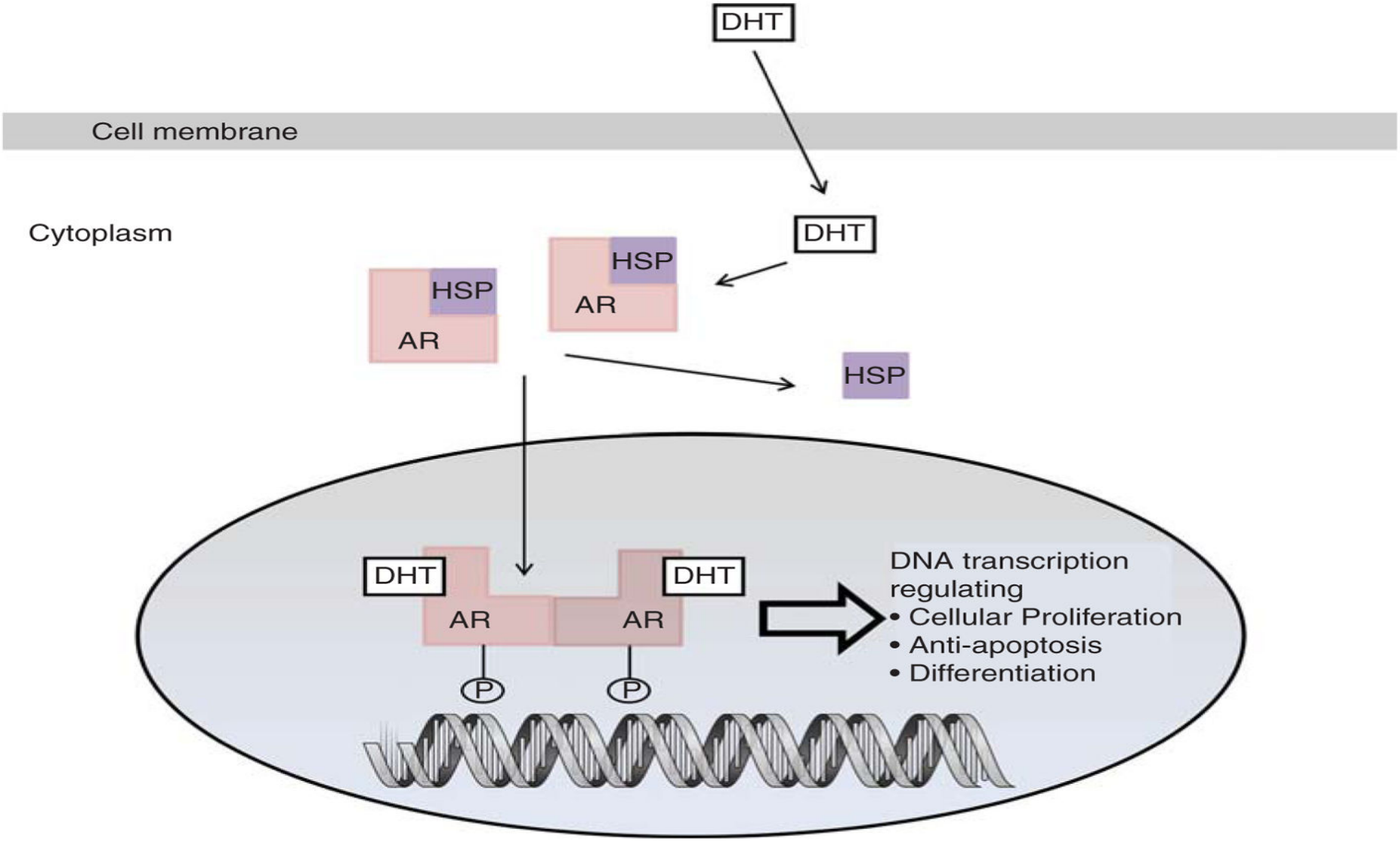
- Mecanismos de Resistencia al Tratamiento Hormonal.
- Estrategias Actuales.
- Posibles Estrategias Futuras.

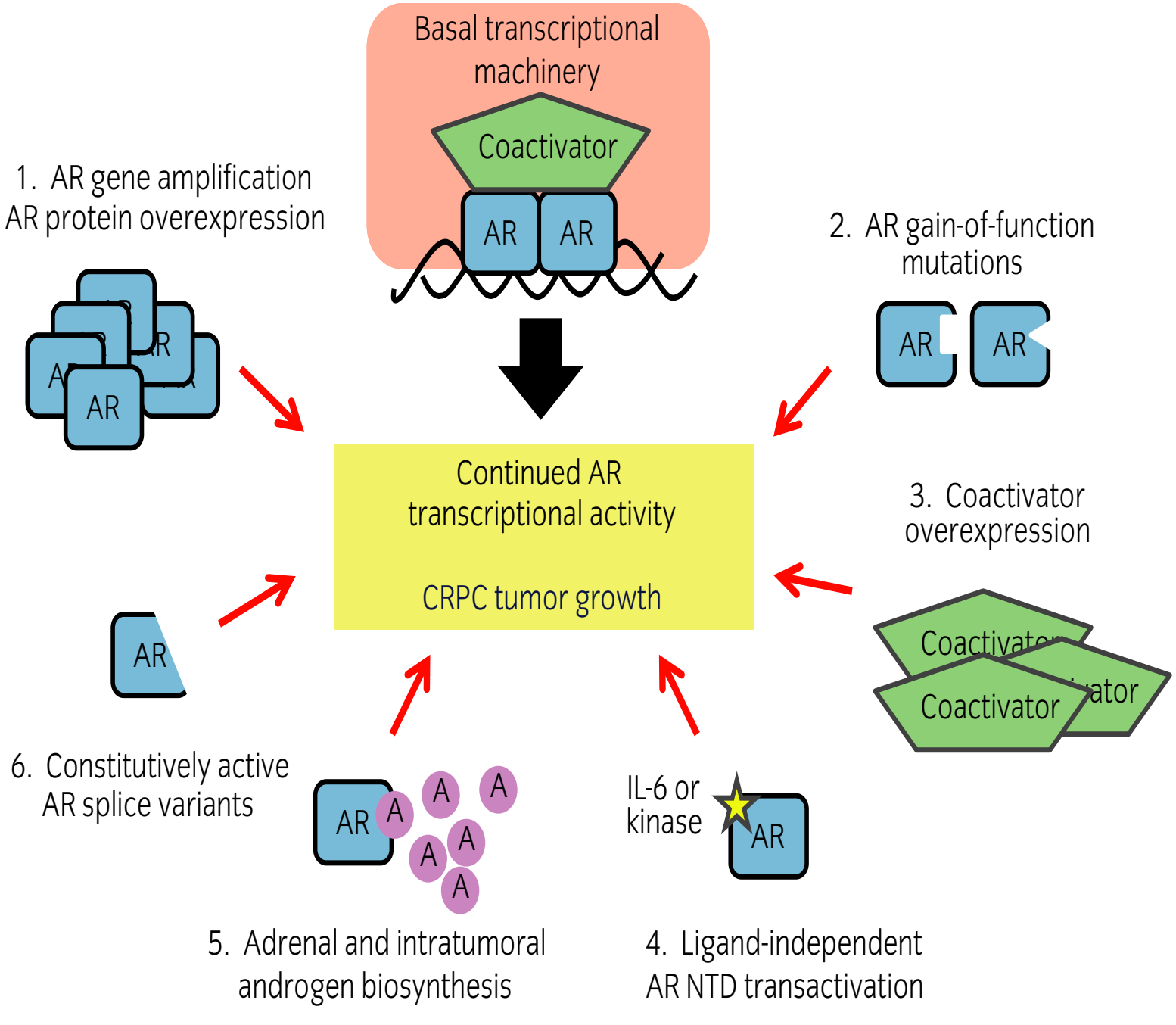


Biology of the androgen receptor signaling pathway

AR: Androgen receptor; DHT: Dihydrotestosterone; HSP: Heat-shock protein; P: Phosphorylation.

MECANISMOS DE RESISTENCIA

AL TRATAMIENTO HORMONAL


Basal transcriptional machinery
Coactivator
AR
AR
1. AR gene amplification
AR protein overexpression
AR
AR
2. AR gain-of-function mutations
AR
AR
Continued AR transcriptional activity
CRPC tumor growth
3. Coactivator overexpression
Coactivator
Coactivator
AR
6. Constitutively active AR splice variants
AR
A
A
A
A
A
5. Adrenal and intratumoral androgen biosynthesis
IL-6 or kinase
AR
4. Ligand-independent AR NTD transactivation

Mechanisms of resistance to AR-targeted therapy in prostate cancer.

1. AR splice variants (AR-Vs)

AR-Vs lack a ligand binding domain leading to constitutive activity in the absence of ligands and ligand-independent AR signaling. AR-V7 or ARv567es form dimers with full-length AR, facilitating AR nuclear localization, and decreasing the ability of therapies to inhibit nuclear trafficking. ARv567es confers resistance to enzalutamide, and AR-V7 confers resistance to abiraterone and enzalutamide.

2. AR overexpression

AR overexpression increases AR responses to the low androgen level in the CRPC state, and can be caused by AR gain or amplification. Common in CRPC: 80% of patients have an elevated gene copy number and approx. 30% have high-level amplification. May play more of a role in resistance to enzalutamide versus abiraterone.

3. Increased AR transcriptional activity

Phosphorylation, ubiquitylation, and methylation of the AR can enhance AR transcriptional activity. May mediate resistance to both enzalutamide and abiraterone.

4. Stabilization of the AR

AR antagonists work, in part, by preventing stabilization of the AR-DNA complex. Some proteins mediating stabilization of the AR may be overexpressed at low androgen levels. HER2 and HER3 have been implicated in the stabilization of the AR and increasing AR-DNA binding, and low androgen levels increase HER2 expression. May mediate resistance to enzalutamide and abiraterone.

5. ERG gene rearrangements

Up to 70% of mCRPCs overexpress ERG, and TMPRSS2-ERG is a marker of advanced disease. ERG gene rearrangements may confer resistance via upregulation of AKR1C3 which mediates increased androgen synthesis. Implicated in resistance to abiraterone.

6. AR mutations

Mutations in exon 8 alter the steroid binding pockets of the AR, allowing AR antagonists to take on an agonist confirmation. F876L mutation confers resistance to enzalutamide and ARN-509 by converting these agents into partial agonists. T877A mutation has been associated with resistance to abiraterone.

7. Increased steroidogenesis

After ADT, increased intratumoral synthesis of testosterone and DHT from weak androgens produced by the adrenal glands, and possible *de novo* synthesis from cholesterol, can cause AR reactivation. mCRPC shifts from being endocrine-driven to paracrine-driven. Abiraterone treatment selects for cells that have increased intratumoral expression of CYP17A1, and are therefore able to synthesize androgens *de novo*.

8. Alternate signal transduction pathways

Resistance to AR-targeted agents in prostate cancer cells may be mediated by activation of alternative signaling pathways that trigger cell survival and proliferation, such as NF-kB, PI3K-AKT, and glucocorticoid receptor.

9. Loss of AR: small cell and neuroendocrine carcinoma of the prostate

NEPC may be linked with resistance to AR inhibition. Neuroendocrine cells normally regulate growth, differentiation and secretion in the prostate and these cells lack expression of the AR. A subset of patients with loss of AR expression may be resistant to AR-targeted therapy.

ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; ERG, ETS-related gene; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine carcinoma of the prostate.

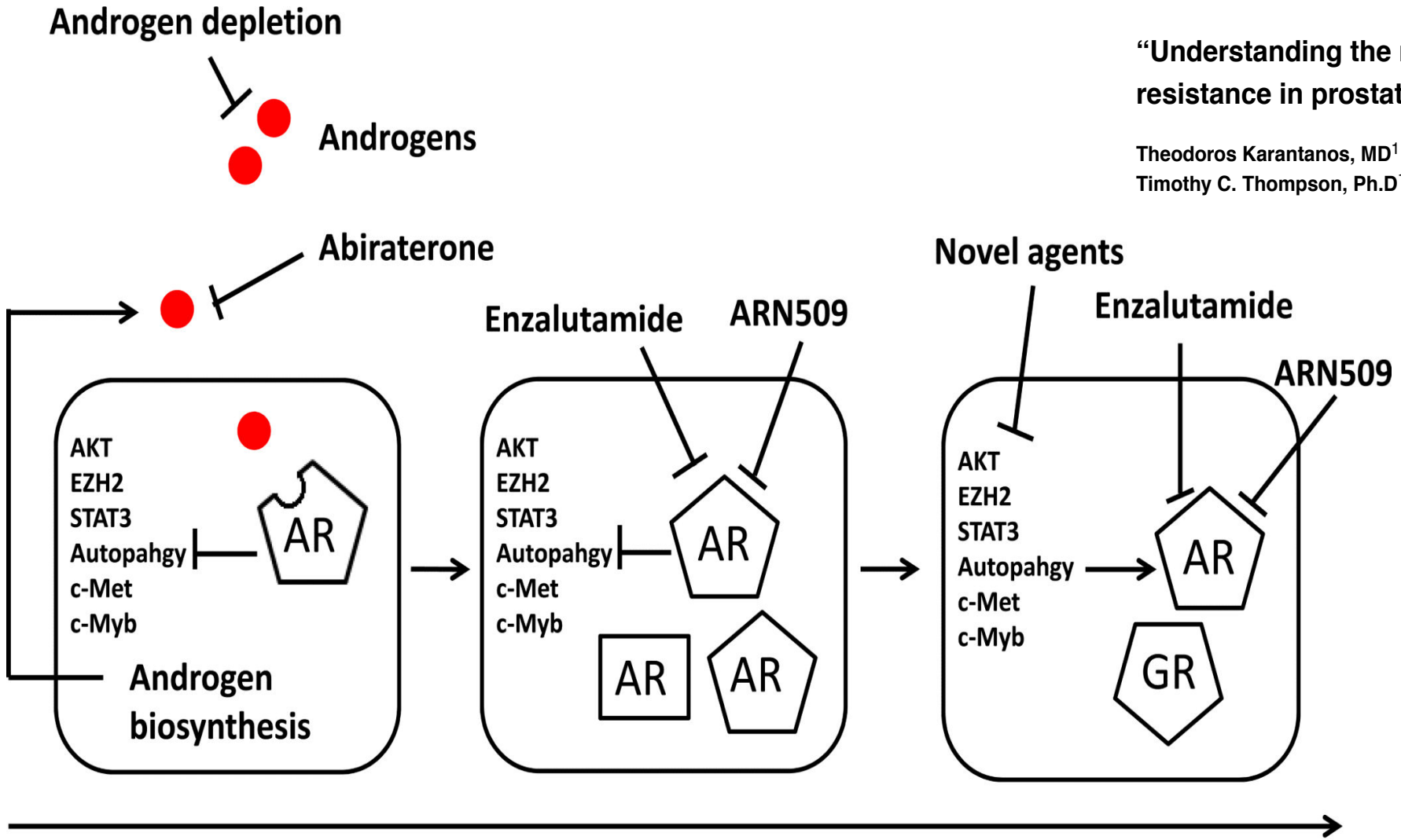
Proposed mechanisms of resistance to abiraterone and enzalutamide.

Abiraterone	**Enzalutamide**
AR amplification/overexpression	AR amplification/overexpression
AR mutations	AR mutations
AR activation by exogenous corticosteroids and steroid precursors upstream CYP17A1	AR splice variants
AR splice variants	Glucocorticoid receptor overexpression
Androgen biosynthesis pathway upregulation	Intracrine synthesis of androgens
Glucocorticoid receptor overexpression	Crosstalk with growth factor
Intracrine synthesis of androgen	Neuroendocrine transformation
Neuroendocrine transformation	Autophagy induction
Autophagy induction	Immune evasion
Immune evasion	

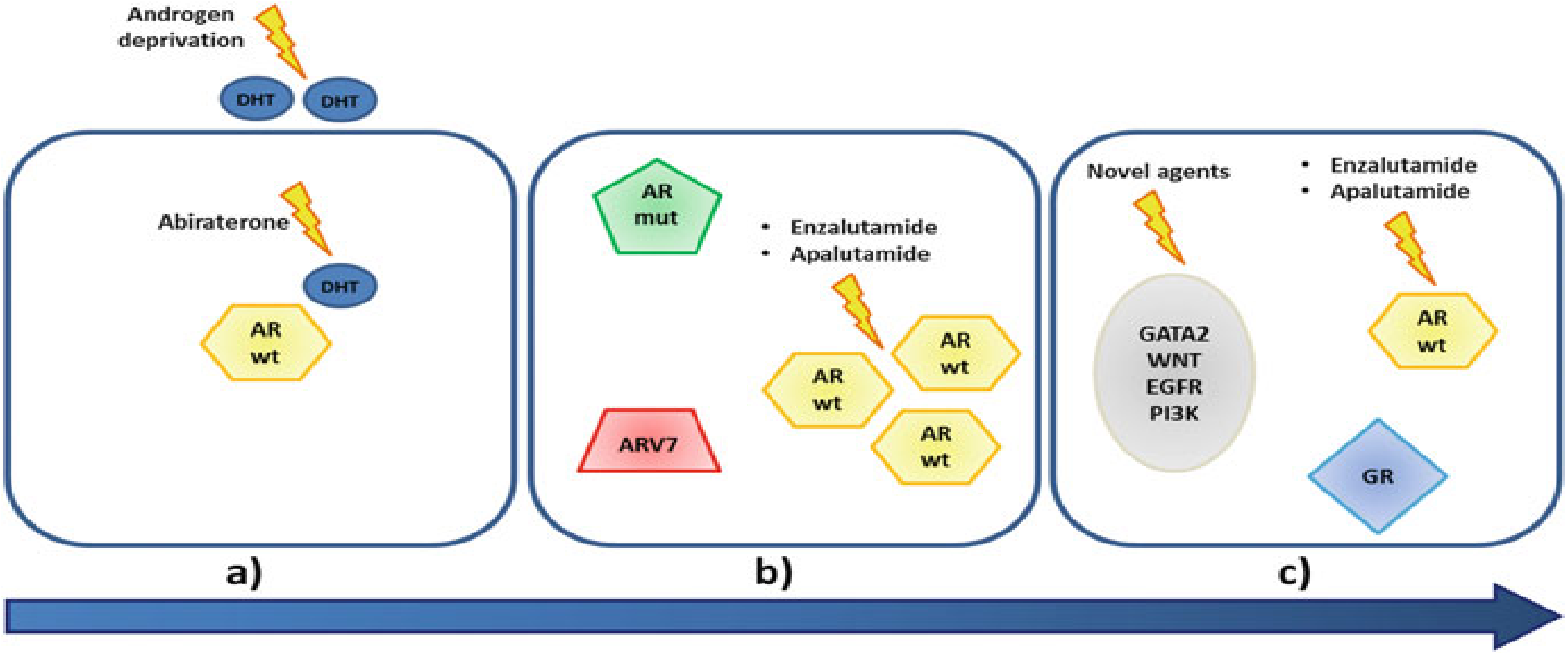
Eur Urol. 2015 March ; 67(3): 470–479. doi:10.1016/j.eururo.2014.09.049.

"Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level"

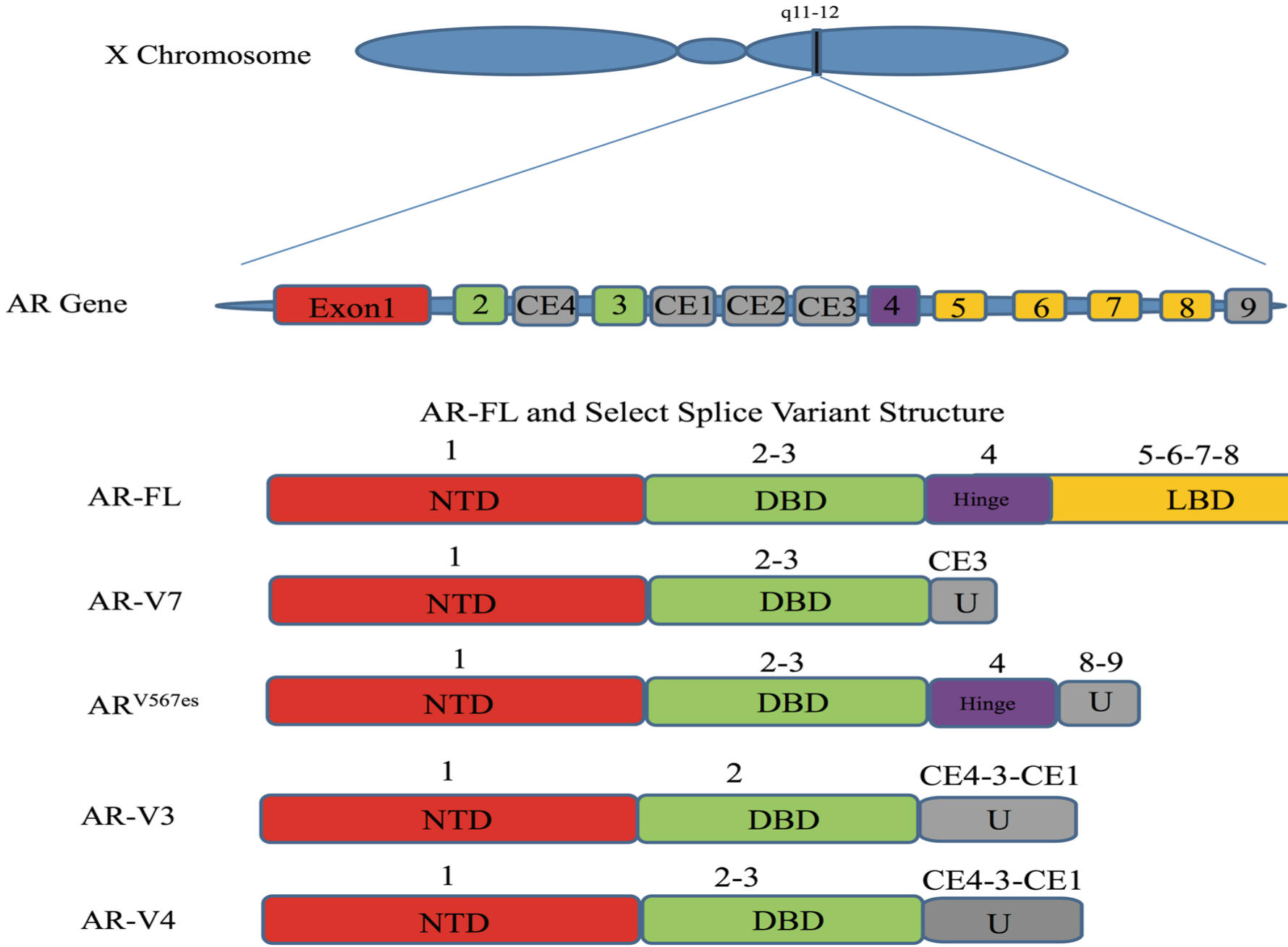
Theodoros Karantanos, MD[1], Christopher Evans, MD[2], Bertrand Tombal, MD, Ph.D[3], Timothy C. Thompson, Ph.D[1], Rodolfo Montironi, MD[4], and William B. Isaacs, Ph.D[5]



- Androgen biosynthesis at the tumor microenvironment
- AR mutations
- AR amplifications
- AR variants
- GR upregulation
- Alternative oncogenic signaling induction



Prostatic adenocarcinoma could escape from androgen deprivation and anti-androgenic therapies, through different mechanisms: (**a**) androgen biosynthesis, (**b**) AR amplification, AR point mutations (AR mut), AR truncated variants (es. ARV7), (**c**) expression of glucocorticoid receptor (GR) and other alternative oncogenic pathways (GATA-2, WNT/Bcatenin, EGFR, PI3K/Akt)

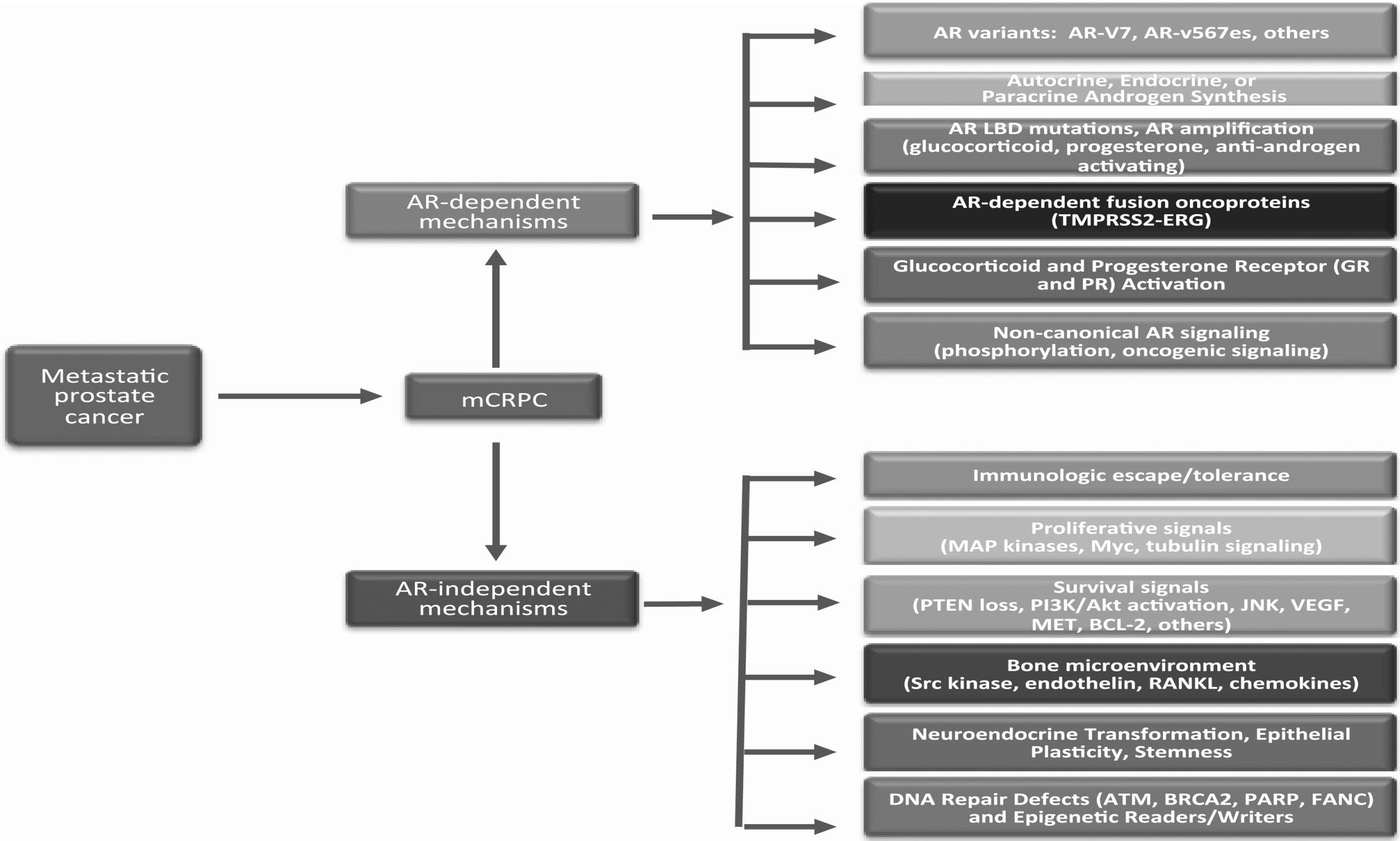

X Chromosome
q11-12
AR Gene
Exon1
2
CE4
3
CE1
CE2
CE3
4
5
6
7
8
9
AR-FL and Select Splice Variant Structure
AR-FL
1
NTD
2-3
DBD
4
Hinge
5-6-7-8
LBD
AR-V7
1
NTD
2-3
DBD
CE3
U
AR^V567es
1
NTD
2-3
DBD
4
Hinge
8-9
U
AR-V3
1
NTD
2
DBD
CE4-3-CE1
U
AR-V4
1
NTD
2-3
DBD
CE4-3-CE1
U

Gain-of-function AR variants recurrently identified in CRPC.

Variant	Transcriptional activity	Clinical relevance
AR-V7 (AR3)	Constitutive	• Resistance to ADT, enzalutamide and abiraterone • Short time to disease relapse after radical prostatectomy and more rapid progression to CRPC • Poor PSA response, short progression-free survival, short overall survival and short cancer-specific survival of CRPC patients
AR-V567es (AR-V12)	Constitutive	• Resistance to ADT • Enriched in CRPC and metastases
AR-V3	Constitutive	• Resistance to ADT and abiraterone • Short progression-free survival of CRPC patients
AR-V1	Dependent on cell context	• Enriched in CRPC and metastases
AR-V9	Dependent on cell context	• Resistance to ADT and abiraterone • Short progression-free survival of CRPC patients

Activating androgen receptor mutations recurrently identified in CRPC.

Mutation	Aberrant effect
T878A	Activated by progesterone, estrogen, flutamide, bicalutamide, enzalutamide and apalutamide
W742C	Activated by bicalutamide, flutamide
H875Y	Activated by estrogen, progesterone, glucocorticoids, adrenal androgens, bicalutamide, flutamide, enzalutamide and apalutamide
F877L	Activated by flutamide, apalutamide and enzalutamide
L702H	Activated by glucocorticoids

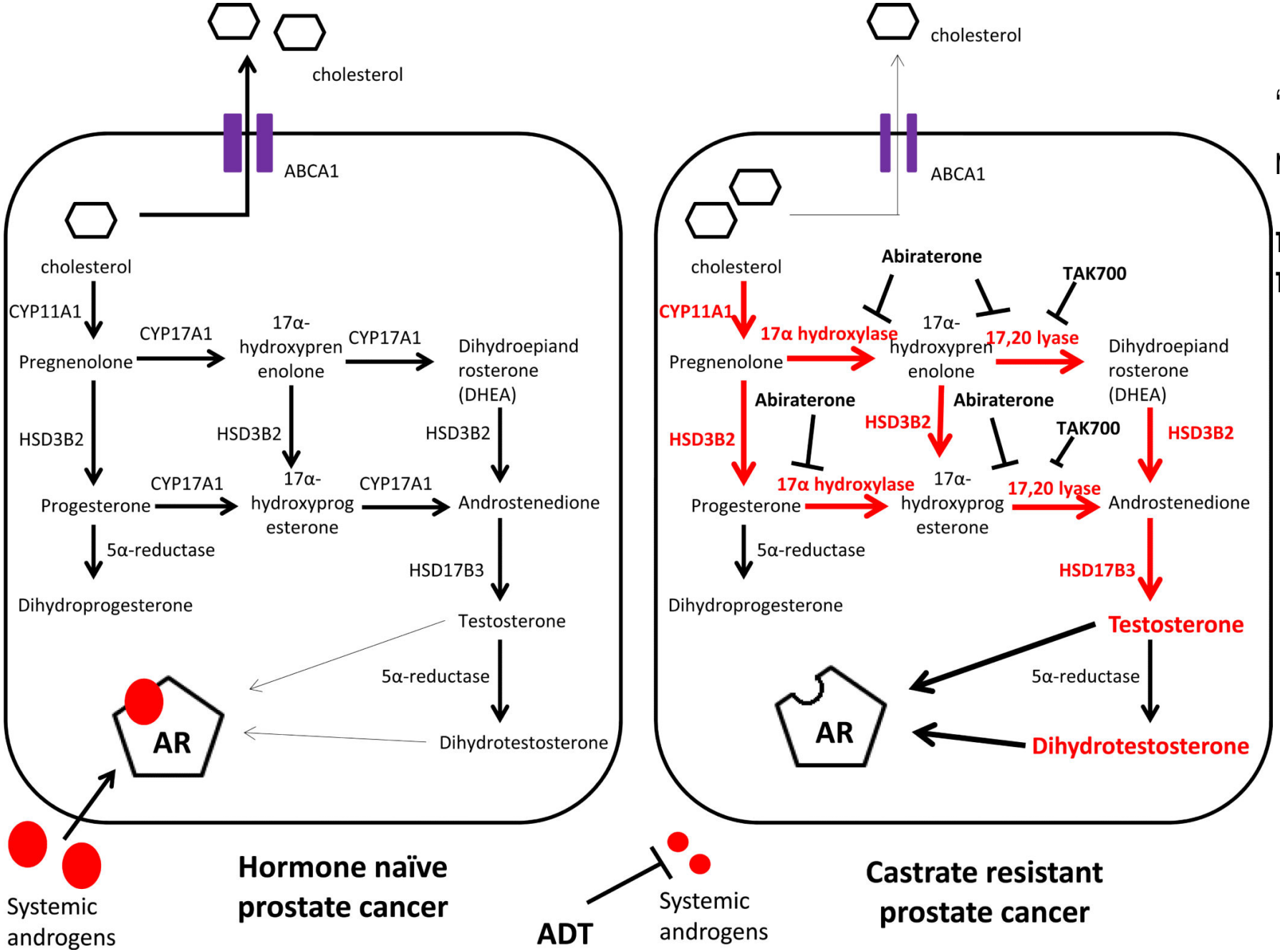

Metastatic prostate cancer
mCRPC
AR-dependent mechanisms
AR-independent mechanisms
AR variants: AR-V7, AR-v567es, others
Autocrine, Endocrine, or Paracrine Androgen Synthesis
AR LBD mutations, AR amplification (glucocorticoid, progesterone, anti-androgen activating)
AR-dependent fusion oncoproteins (TMPRSS2-ERG)
Glucocorticoid and Progesterone Receptor (GR and PR) Activation
Non-canonical AR signaling (phosphorylation, oncogenic signaling)
Immunologic escape/tolerance
Proliferative signals (MAP kinases, Myc, tubulin signaling)
Survival signals (PTEN loss, PI3K/Akt activation, JNK, VEGF, MET, BCL-2, others)
Bone microenvironment (Src kinase, endothelin, RANKL, chemokines)
Neuroendocrine Transformation, Epithelial Plasticity, Stemness
DNA Repair Defects (ATM, BRCA2, PARP, FANC) and Epigenetic Readers/Writers

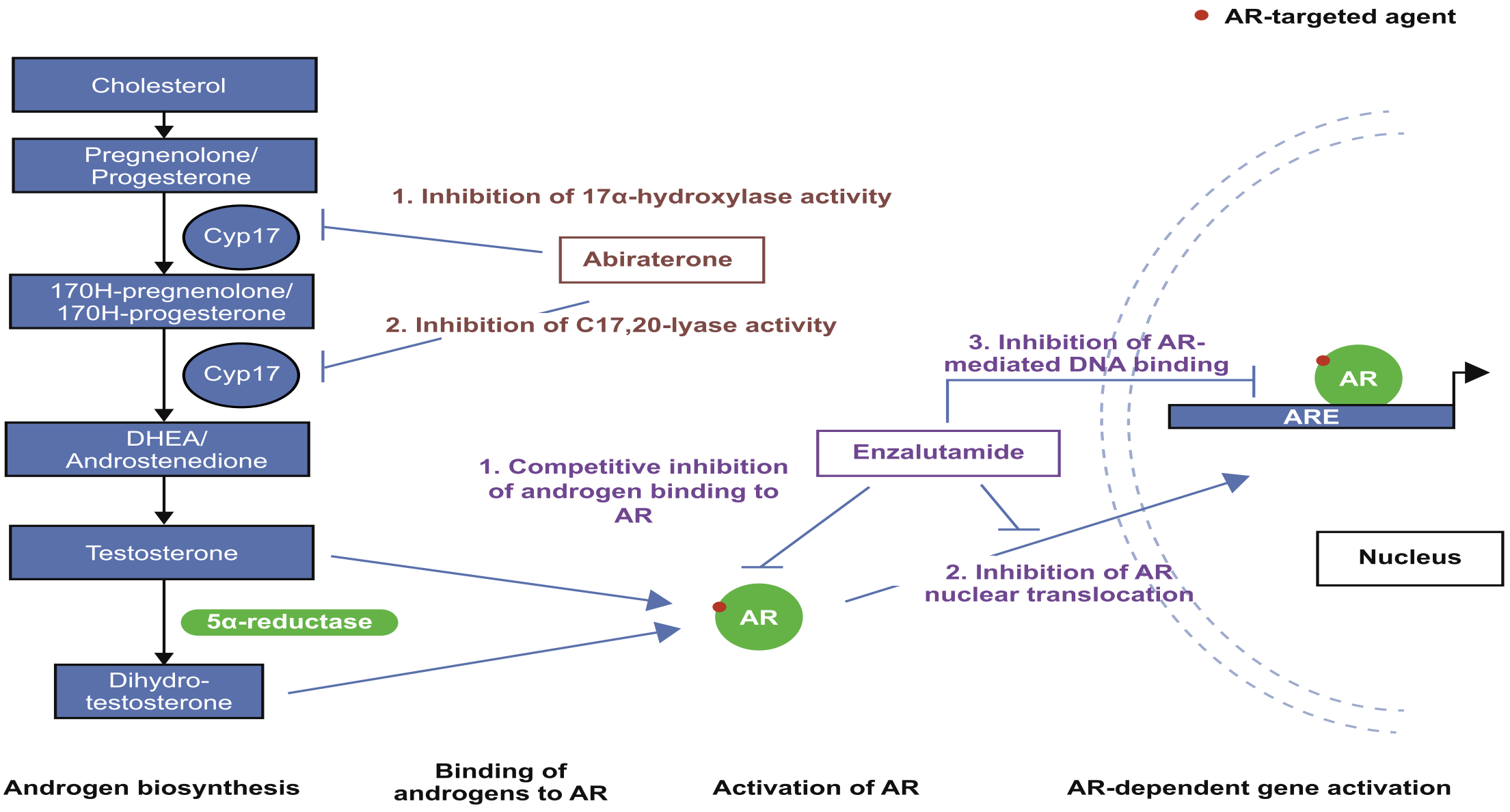
ESTRATEGIAS ACTUALES

Eur Urol. 2015 March ; 67(3): 470–479. doi:10.1016/j.eururo.2014.09.049.

"Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level"

Theodoros Karantanos, MD[1], Christopher Evans, MD[2], Bertrand Tombal, MD, Ph.D[3], Timothy C. Thompson, Ph.D[1], Rodolfo Montironi, MD[4], and William B. Isaacs, Ph.D[5]

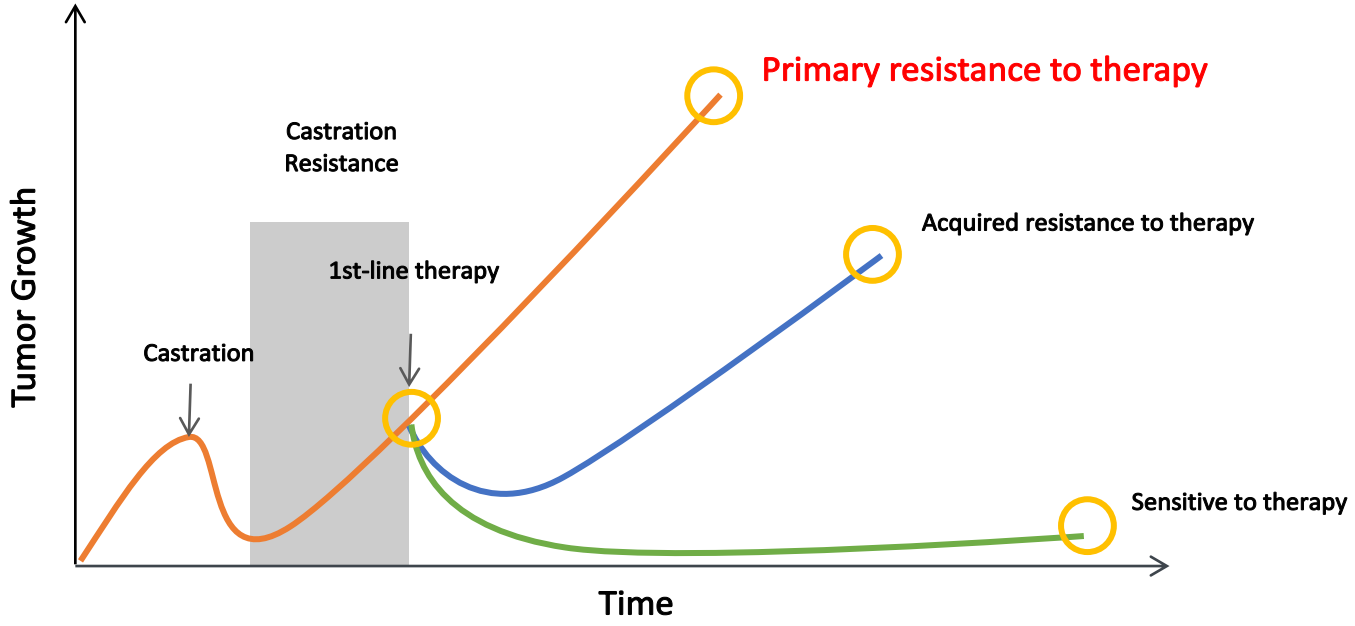




AR-targeted therapies in mCRPC: Mechanisms of action.

Trayectoria de la resistencia al tratamiento endocrino en Cáncer de Próstata

- No todos los pacientes responden al tratamiento, mientras que otros pierden respuesta a lo largo del tiempo:
  - **Resistencia Primaria** (pacientes que son inicialmente refractarios al tratamiento)
  - **Resistencia Adquirida** (pacientes que desarrollan resistencia varios meses después del inicio del tratamiento)



Mukherji D, et al. *Cancer Metastasis Rev.* 2014;33(2-3):555-566.

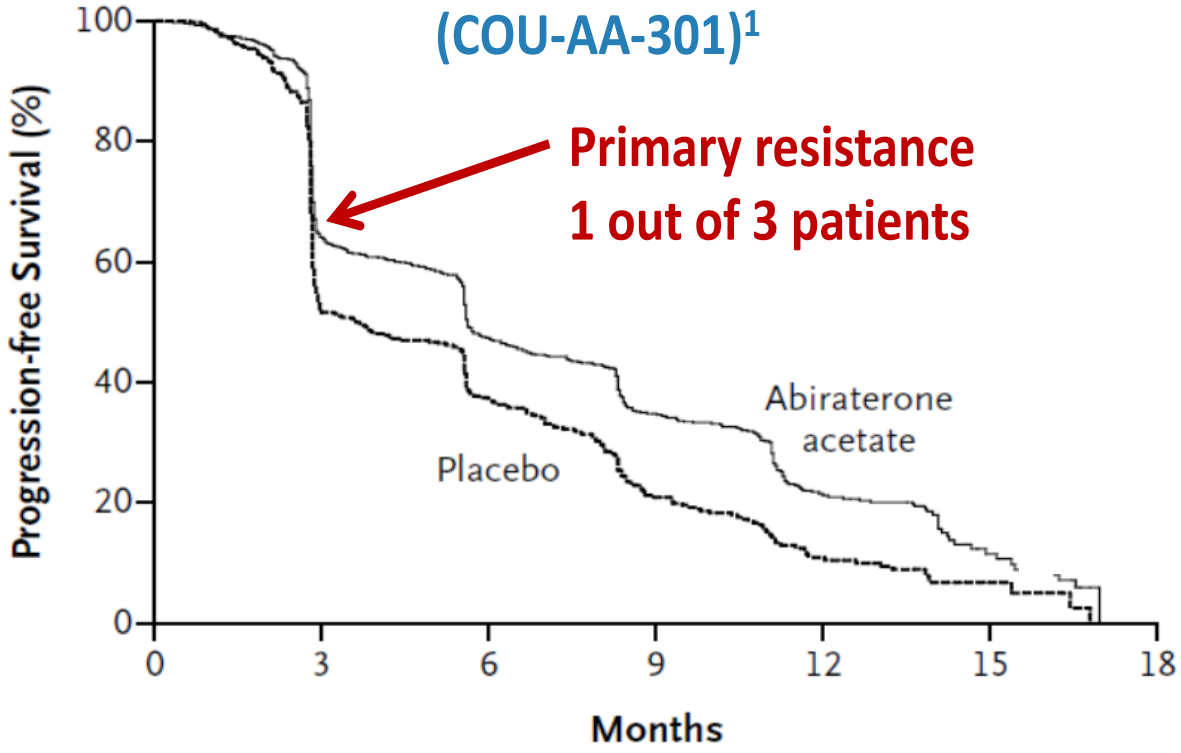
The “Real” Issues

- **Primary resistance to ART**
  - How to identify?
  - Why to identify?
  - What to do in such cases?
- **Monitoring treatment**
  - How frequently?
  - Which modality?
- **Switching treatment**
  - When to switch?
  - What will the next treatment be?

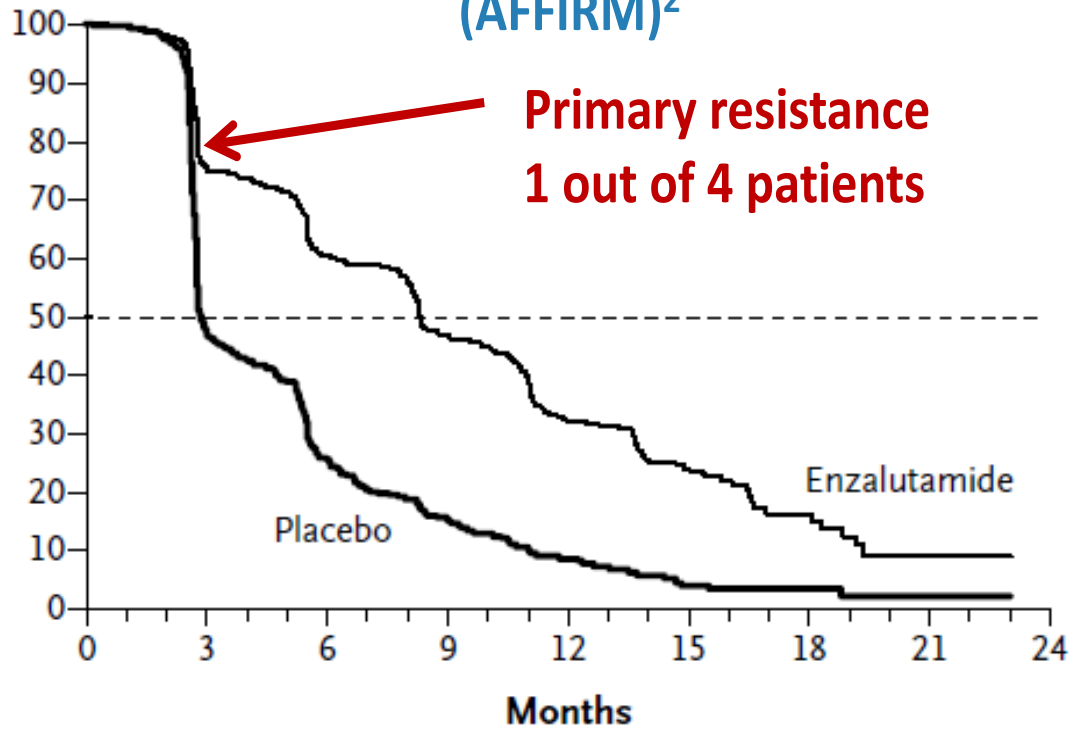
Primary Resistance to ART

Radiological progression-free survival (rPFS)

ABI + P
(COU-AA-301)[1]



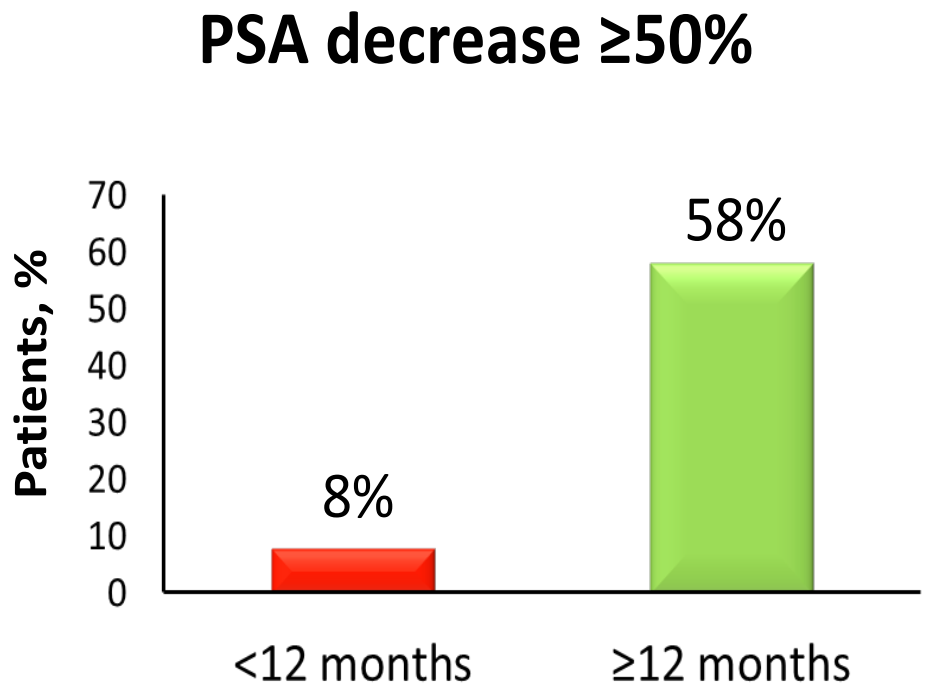
ENZA ± P
(AFFIRM)[2]



1. De Bono JS et al. N Engl J Med. 2011;364:1995-2005; 2. Scher H et al. N Engl J Med. 2012;367:1187-97.

Primary Resistance to ART

How to Identify?



- Short response (<1 year) to first ADT may predict poor response to subsequent ART[1]
- Perhaps the only reliable clinical parameter
- The other factor to consider is the 'aggressiveness' of cancer

Retrospective cohort of 173 patients, including 57 treated with ENZA in AFFIRM phase III trial[1]

1. Loriot Y et al. Eur J Cancer. 2015;51:1946-52.

EUROPEAN UROLOGY 70 (2016) 724–731

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Benjamin L. Maughan and Mario A. Eisenberger on pp. 732–733 of this issue

Prostate-specific Antigen Decline After 4 Weeks of Treatment with Abiraterone Acetate and Overall Survival in Patients with Metastatic Castration-resistant Prostate Cancer

Pasquale Rescigno, David Lorente, Diletta Bianchini, Roberta Ferraldeschi, Michael P. Kolinsky, Spyridon Sideris, Zafeiris Zafeiriou, Semini Sumanasuriya, Alan D. Smith, Niven Mehra, Anuradha Jayaram, Raquel Perez-Lopez, Joaquin Mateo, Chris Parker, David P. Dearnaley, Nina Tunariu, Alison Reid, Gerhardt Attard, Johann S. de Bono *

European Journal of Cancer 61 (2016) 44–51

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Early PSA response is an independent prognostic factor in patients with metastatic castration-resistant prostate cancer treated with next-generation androgen pathway inhibitors

Alina Fuerea, Giulia Baciarello, Anna Patrikidou, Laurence Albigès, Christophe Massard, Mario Di Palma, Bernard Escudier, Karim Fizazi, Yohann Loriot*

- **PSA is a pharmacodynamic measure of AR signaling[1]**
  → PSA falls when AR signaling is blocked

- **No PSA decline ≥30% at 1 month with ART associated with poor OS[1-2]** → Imaging

1. Rescigno P et al. Eur Urol. 2016:724-731; 2. Fuerea A et al. Eur J Cancer. 2016;61:44-51.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

Original Investigation

Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer

Emmanuel S. Antonarakis, MD; Changxue Lu, PhD; Brandon Luber, ScM; Hao Wang, PhD; Yan Chen, PhD; Mary Nakazawa, MHS; Rosa Nadal, MD; Channing J. Paller, MD; Samuel R. Denmeade, MD; Michael A. Carducci, MD; Mario A. Eisenberger, MD; Jun Luo, PhD

Antonarakis ES et al. N Engl J Med. 2014;371:1028-38; Antonarakis ES et al. JAMA Oncol. 2015;1:582-91.

Primary Resistance to ART

Why to Identify?

- Not all patients will benefit from ART
- Likelihood of increased primary resistance if more lines of previous therapy
- Despite this factor … clinicians will use ART as their preferred modality in **ALL** cases of mCRPC
- Whilst ART is the optimum therapy for the **MAJORITY** of mCRPC cases, it is **NOT** the optimum therapy for **ALL** cases
- The challenge for the uro-oncologist is to use clinical factors to decide which patients are likely to have primary resistance to ART and offer **chemotherapy as the preferred option** for these cases

Primary Resistance to ART
What to Do in Such Cases?

- Discuss with the patient the proposed sequencing
  - DOC first
- Explain the concept of chemotherapy continuum
  - If disease progression after 3 cycles of DOC → switch to CABA
- Address the concern factors associated with chemotherapy
- If ART given, then ensure frequent and relevant monitoring
  - Patient should not loose the opportunity of receiving the next therapy

Monitoring Treatment

- Monitoring in real life practice often is dictated by practical considerations including the radiological modalities available

- Guidelines usually recommend:
  - **Frequency and modality**
    - Clinical: every cycle
    - Biochemical: PSA every 4 weeks
    - **Radiological: every 3 months if other parameters stable, otherwise earlier**

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

Table 4. Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

Measure*	PCWG2 Frequency (2008)	PCWG3 Frequency (2015)†
Clinical		
Symptoms/ performance status	Every cycle	Retained
Blood-based markers		
PSA	By cycle (every 3 or 4 weeks)	Retained
ALK, LDH	By cycle (every 3 or 4 weeks)	Retained
Serum chemistry, CBC	Not addressed	By cycle (every 3 to 4 weeks)
Circulating tumor cells	Not addressed	By cycle (every 3 to 4 weeks) if available
Imaging		
Bone scans	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
CT/MRI	Every 12 weeks	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks†
Patient-reported outcomes	Not addressed	By cycle (every 3 to 4 weeks)
Analgesic consumption (opioids/no opioids)	Not addressed	By cycle (every 3 to 4 weeks)

Abbreviations: ALK, alkaline phosphatase; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate Cancer Clinical Trials Working Group 2; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

*All measures should be assessed at baseline to determine changes over time.

†There may be exceptions to these suggestions: in nonmetastatic castration-resistant prostate cancer trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (> 2 to 3 years of clinical benefit and no signs of clinical or biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months).

Scher HI et al, J Clin Oncol. 2016 Feb 22.

mCRPC Patient on ART (ABI or ENZA)

- Is it important to do radiological monitoring if the patient is symptomatically doing well and PSA is controlled on ART?

YES

Prostate Cancer and Prostatic Diseases (2017) 00, 1–7
www.nature.com/pcan

ORIGINAL ARTICLE

Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: *post hoc* analysis of PREVAIL

AH Bryce[1], JJ Alumkal[2], A Armstrong[3], CS Higano[4], P Iversen[5], CN Sternberg[6], D Rathkopf[7], Y Loriot[8], J de Bono[9], B Tombal[10], S Abhyankar[11,15], P Lin[12], A Krivoshik[13], D Phung[14] and TM Beer[2]

BACKGROUND: Advanced prostate cancer is a phenotypically diverse disease that evolves through multiple clinical courses. PSA level is the most widely used parameter for disease monitoring, but it has well-recognized limitations. Unlike in clinical trials, in practice, clinicians may rely on PSA monitoring alone to determine disease status on therapy. This approach has not been adequately tested.

METHODS: Chemotherapy-naive asymptomatic or mildly symptomatic men ($n=872$) with metastatic castration-resistant prostate cancer (mCRPC) who were treated with the androgen receptor inhibitor enzalutamide in the PREVAIL study were analyzed *post hoc* for rising versus nonrising PSA (empirically defined as >1.05 vs $\leqslant 1.05$ times the PSA level from 3 months earlier) at the time of radiographic progression. Clinical characteristics and disease outcomes were compared between the rising and nonrising PSA groups.

RESULTS: Of 265 PREVAIL patients with radiographic progression and evaluable PSA levels on the enzalutamide arm, nearly one-quarter had a nonrising PSA. Median progression-free survival in this cohort was 8.3 months versus 11.1 months in the rising PSA cohort (hazard ratio 1.68; 95% confidence interval 1.26–2.23); overall survival was similar between the two groups, although less than half of patients in either group were still at risk at 24 months. Baseline clinical characteristics of the two groups were similar.

CONCLUSIONS: Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients treated with enzalutamide. As restaging in advanced prostate cancer patients is often guided by increases in PSA levels, our results demonstrate that disease progression on enzalutamide can occur without rising PSA levels. Therefore, a disease monitoring strategy that includes imaging not entirely reliant on serial serum PSA measurement may more accurately identify disease progression.

Prostate Cancer and Prostatic Diseases advance online publication, 24 January 2017; doi:10.1038/pcan.2016.71

Non-rising PSA at radiographic progression is a common phenomenon in mCRPC patients

Of 265 PREVAIL patients with radiological progression and evaluable PSA levels on enzalutamide,

65 (24.5%) had a non rising PSA

Bryce AH et al. Prostate Cancer Prostatic Dis. 2017;20:221-7.

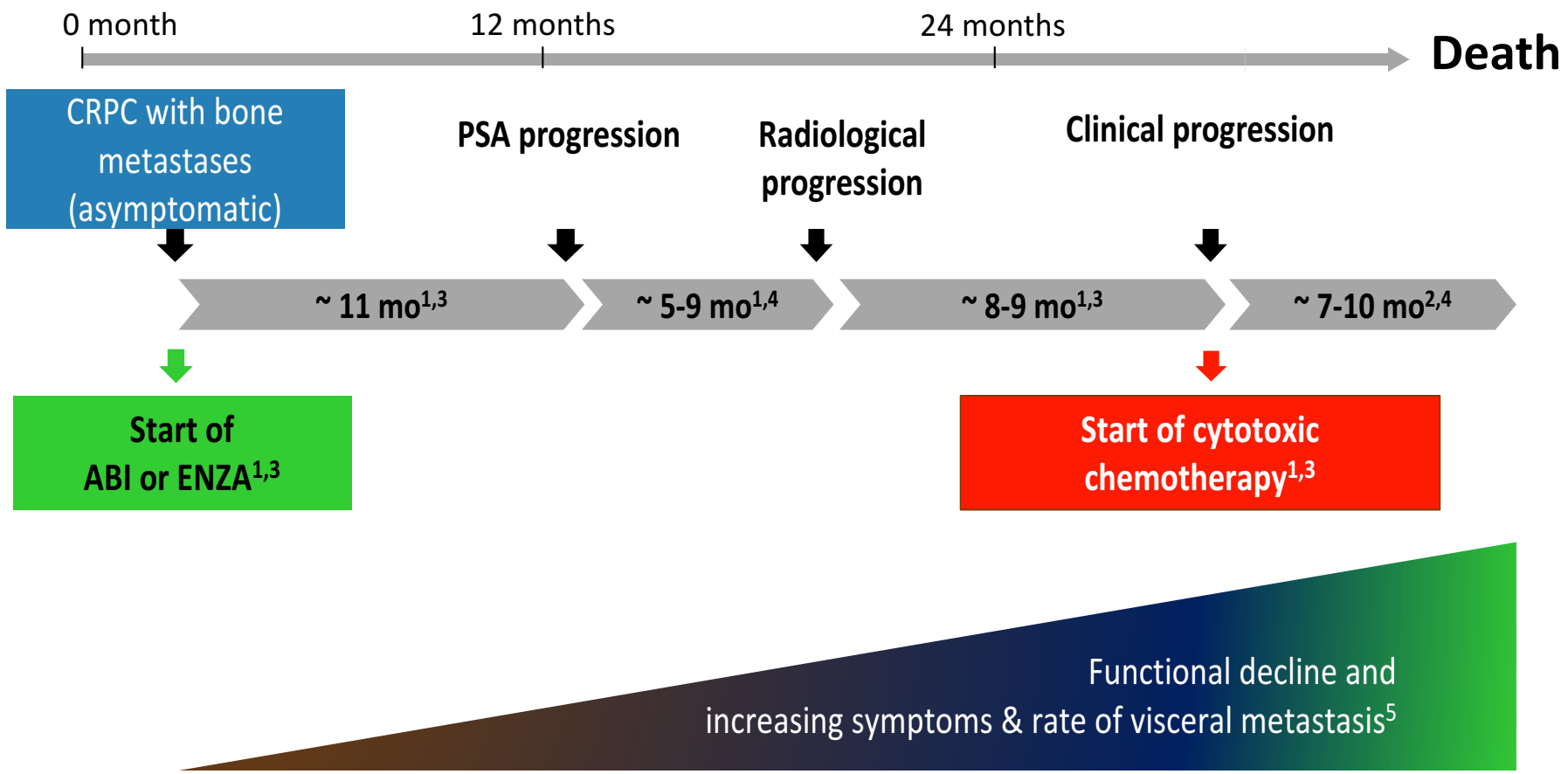
When to Switch Treatment?

- Generally accepted view is that 2 out of the following 3 factors should be met[1]:
  - PSA progression
  - Radiological progression
  - Symptomatic progression

- However, unequivocal radiological progression which is clinically meaningful on its own warrants change in therapy

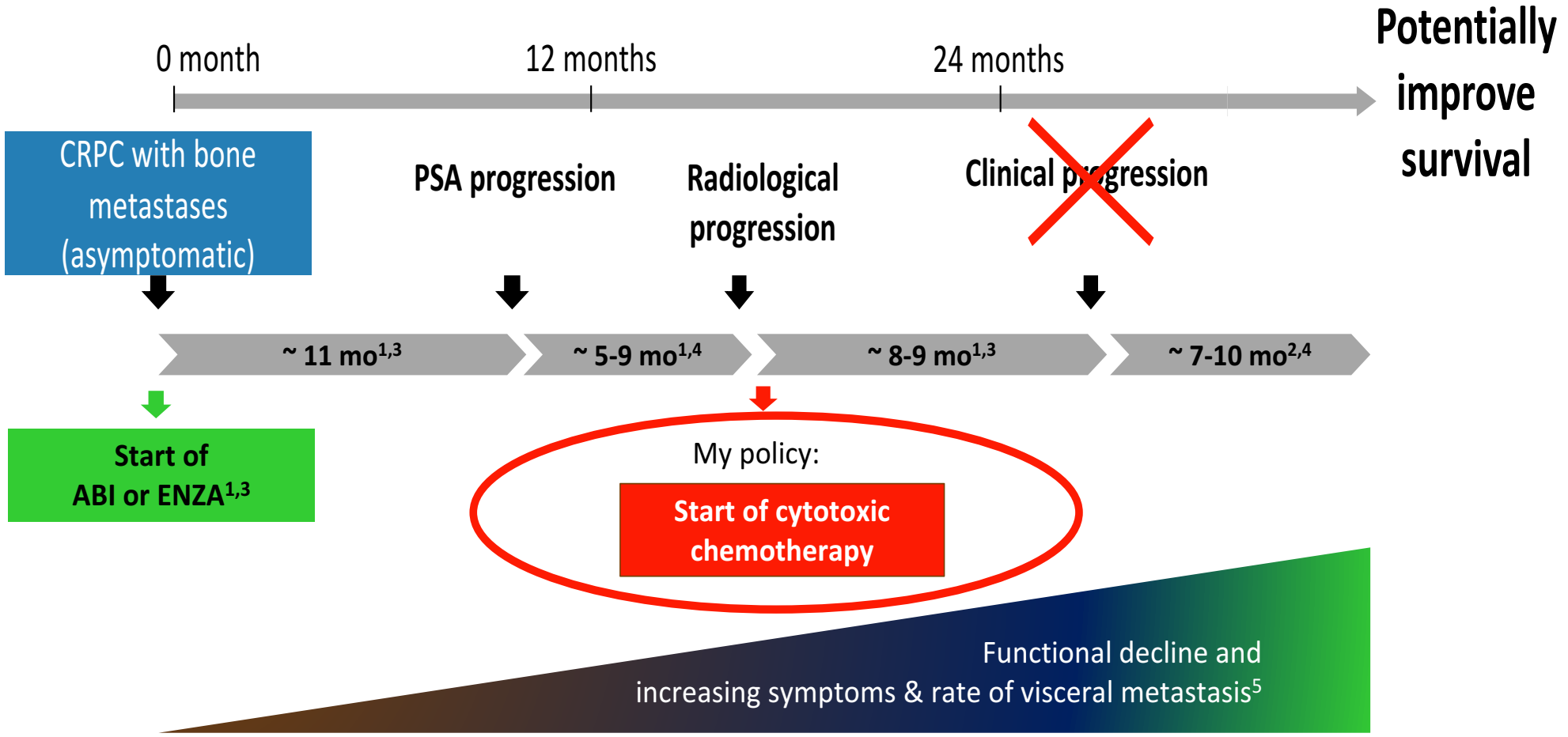
1. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2018. (http://uroweb.org).

A Closer Look at Time to Events in COU-AA-302 and PREVAIL Studies



1. Ryan CJ et al. N Engl J Med. 2013;368:138-48; 2. Ryan CJ et al. Lancet Oncol. 2015;16:152-60; 3. Beer TM et al. N Engl J Med. 2014;371:424-33; 4. Beer TM et al. Eur Urol. 2017;71:151-4; 5. Pezaro CJ et al. Eur Urol. 2014;65:270-3.

A Closer Look at Time to Events in COU-AA-302 and PREVAIL Studies



1. Ryan CJ et al. N Engl J Med. 2013;368:138-48; 2. Ryan CJ et al. Lancet Oncol. 2015;16:152-60; 3. Beer TM et al. N Engl J Med. 2014;371:424-33; 4. Beer TM et al. Eur Urol. 2017;71:151-4; 5. Pezaro CJ et al. Eur Urol. 2014;65:270-3.

Progression on ART in mCRPC: Cross-Resistance Between ART

- Poor response to ENZA if progression on ABI[1]
- Poor response to ABI if progression on ENZA[1-2]

- **NICE (UK) does not permit use of sequential ART if there is progression on first ART[3]**

- Preferred treatment option if patient fit → chemotherapy

1. Expert Opin Pharmacother. 2015;16:473-85; 2. Attard G et al. J Clin Oncol. 2017;35(suppl):abstract 5004 (podium presentation);
3. https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer

Cross-Resistance Between ART

Poor response to ABI if progression on ENZA

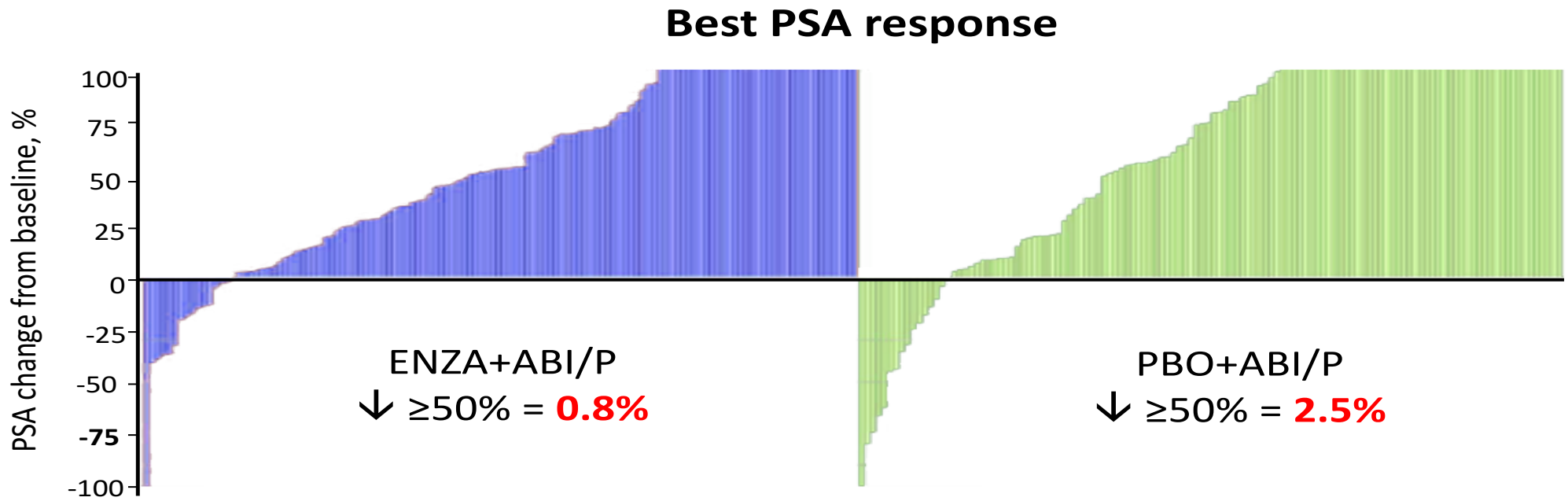
Author	Year published	N patients	Duration of 2nd treatment	↓ PSA ≥ 50%	Median PFS
No prior ENZA					
De Bono et al.[1] (COU-AA-302)	2011	797	8 mos	29%	5.8 mos
ENZA→ABI					
Loriot et al.[2]	2013	38	3 mos	8%	2.7 mos
Noonan et al.[3]	2013	30	13 wks	3%	3.6 mos

[1] prospective randomized trial of ABI/P vs P in mCRPC (post-DOC);
[2-3] trials are retrospective studies in mCRPC pts (post-DOC).

1. De Bono J et al. N Engl J Med. 2011;364:1995-2005; 2. Loriot Y et al. Ann Oncol. 2013;24:1807-12; 3. Noonan KL et al. Ann Oncol. 2013;24:1802-7.

Cross-Resistance Between ABI and ENZA

- PLATO – Prospective, phase IV, double-blind, PBO-controlled study in 251 chemo-naïve mCRPC patients with PSA response to ENZA >3 months
- Randomized at PSA progression to ENZA+ABI/P vs PBO+ABI/P
- PFS* (primary endpoint): 5.7 vs 5.6 months, *P*=0.22



Attard G et al. J Clin Oncol. 2017;35(suppl):abstract 5004 (podium presentation) - NCT01995513.

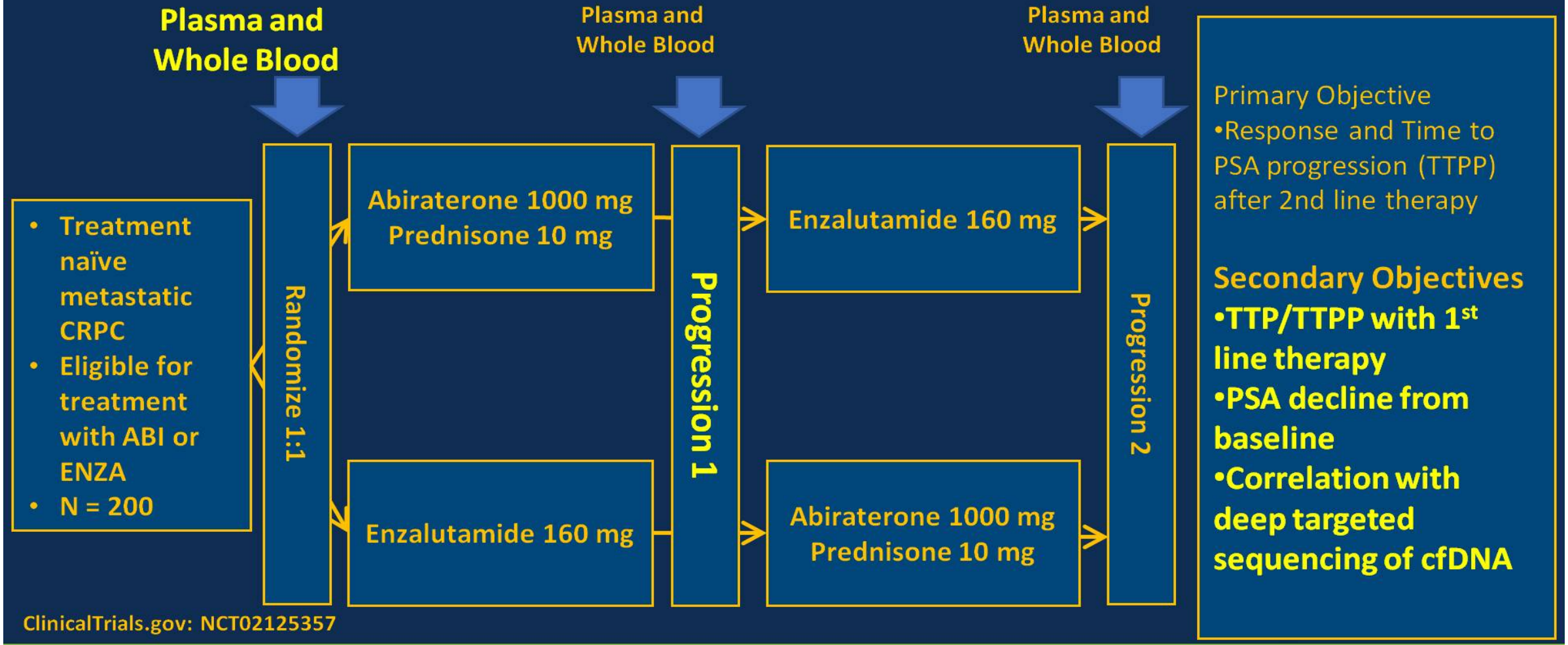
A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Study Schema



Methods: Circulating Tumor DNA

- Targeted sequencing: all patients
  - Plasma cell free DNA and germline (WBC)
  - 73 CRPC-related genes (all exons) including
    - Prostate cancer drivers (e.g. AR, SPOP, NKX3.1, FOXA1)
    - Cell cycle (e.g. TP53, RB1, CDKN1B, CDKN2A)
    - DNA repair (e.g. BRCA1/2, FANC family genes, ATM, MSH2/6)
    - PI3K pathway (e.g. PIK3CA, PTEN, AKT1)
- AR gene sequencing (exons, introns, flanking regions) to detect AR gene rearrangements
- Whole exome sequencing in patients with >20% ctDNA

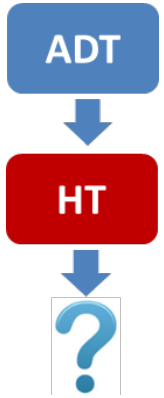
Genomic Correlates with TTP

Genomic Alteration	Median TTP Positive vs Negative* (months)	Univariate		Multivariate***	
		HR	P-value	HR	P-value
BRCA2/ATM truncating mutation	**1.8 vs 8.0**	**6.14 (3.35-11.26)**	**<0.001**	**5.34 (2.84-10.03)**	**<0.001**
TP53 inactivation**	**3.3 vs 10.2**	**2.78 (1.92-4.03)**	**<0.001**	**2.21 (1.38-3.55)**	**0.001**
PI3K pathway	**3.3 vs 10.4**	**2.73 (1.91-3.90)**	**<0.001**	**1.95 (1.31-2.90)**	**<0.001**
AR amplification	**5.0 vs 9.3**	**2.05 (1.43-2.93)**	**<0.001**	1.29 (0.85-2.09)	0.271
RB1 inactivation**	**3.6 vs 8.2**	**2.03 (1.36-3.04)**	**<0.001**	1.45 (0.95-2.21)	0.08
SPOP mutation	7.3 vs 7.4	1.00 (0.51-1.97)	1.00		
AR mutation	6.2 vs 7.4	1.02 (0.53-1.95)	0.95		

Includes patients without detectable ctDNA; ** Mutation, deletion, or rearrangement
*** MVA includes trial arm, presence of quantifiable ctDNA, and clinical prognostic factors (LDH, ALP, Visceral Mets, ECOG PS)

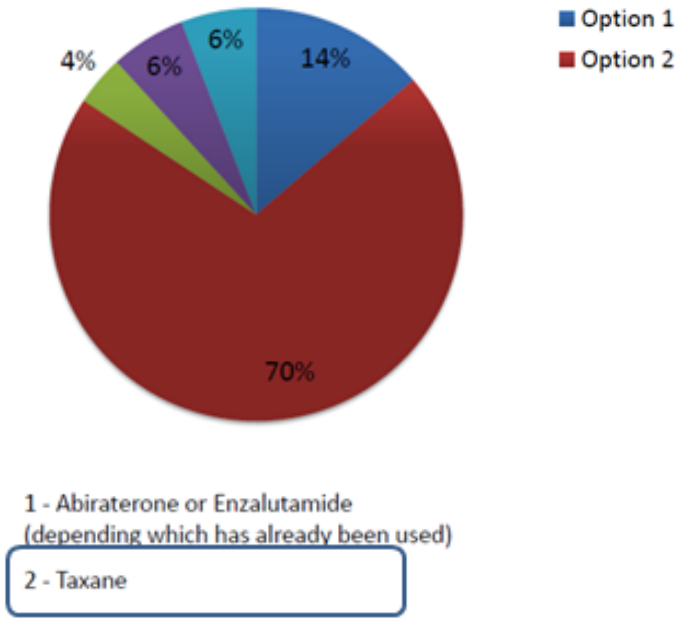
Conclusions

- Higher PSA response with enzalutamide compared to abiraterone + prednisone but with no difference in time to progression or time to PSA progression
- Detection of ctDNA was associated with measures of tumour burden and poor outcomes
- Genomic alterations in *BRCA2/ATM, TP53,* PI3K pathway, *RB1,* and *AR* were associated with earlier progression and primary resistance
- In multivariate analyses including clinical factors, *BRCA2/ATM, TP53* and *PI3K* pathway alterations remained significantly associated with shorter TTP
- *AR* genomic structural rearrangements encoding for truncated AR are detectable in ctDNA from treatment naïve mCRPC and may identify primary resistant disease

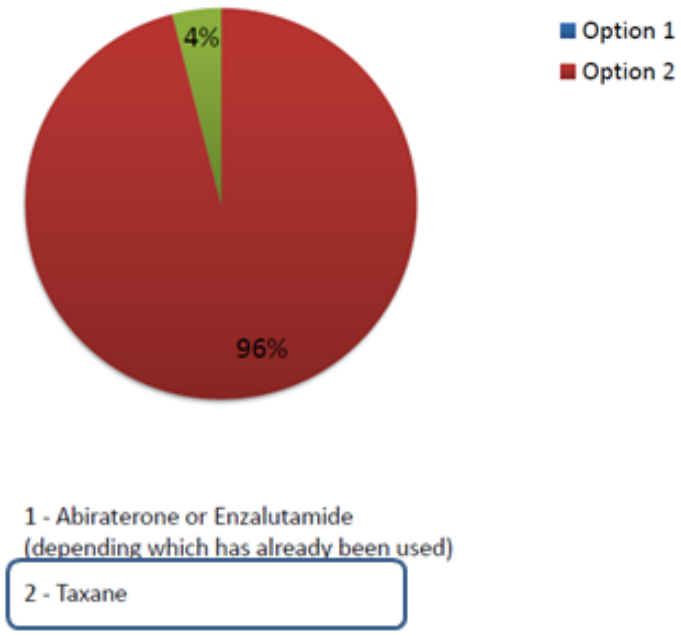


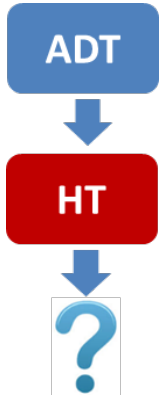
Resistencia primaria a HT

En pacientes con cáncer de próstata asintomático, cuya mejor respuesta a AA/ENZ haya sido la progresión, el 70% de los panelistas elegirían Taxanos como tto de segunda línea



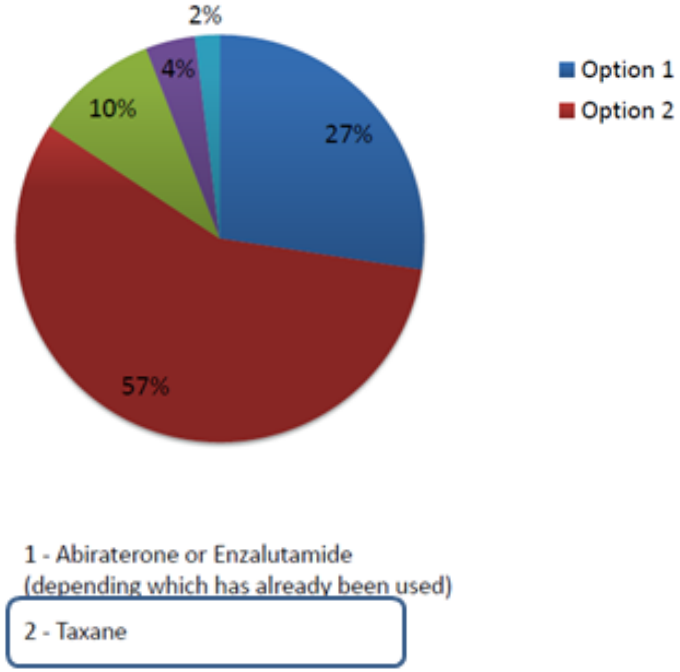
En pacientes con cáncer de próstata sintomatico, cuya mejor respuesta a AA/ENZ haya sido la progresión, el 96% de los panelistas elegirían Taxanos como tto de segunda línea



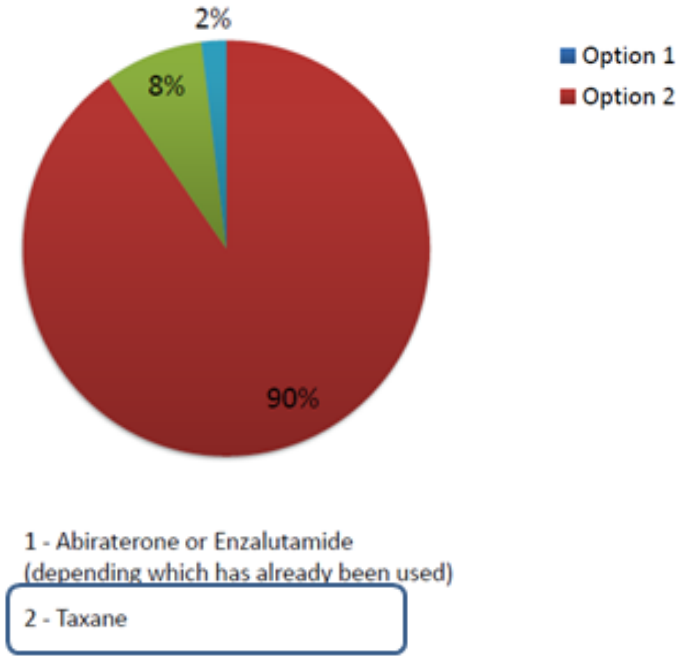


Resistencia adquirida a HT

En pacientes con cáncer de próstata asintomático, que respondieron a AA/ENZ y luego progresaron, el 57% de los panelistas elegirían Taxanos como tto de segunda línea



En pacientes con cáncer de próstata sintomático, que respondieron a AA/ENZy luego progresaron, el 90% de los panelistas elegirían Taxanos como tto de segunda línea



- ESTRATEGIAS FUTURAS

Selected biomarker trials evaluating the clinical utility of AR-V7 in CRPC patients

Therapeutic agents	Trial phase	Description	Key outcomes	Biomarker platform	NCT number
Cabazitaxel vs abiraterone/enzalutamide *[PRIMCAB]*	Phase 2	Randomized open-label trial of cabazitaxel vs abiraterone or enzalutamide in mCRPC patients refractory to enzalutamide or abiraterone, with prospective validation of AR-V7 biomarker	rPFS	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02379390
Cabazitaxel vs abiraterone/enzalutamide *[OZM-054]*	Phase 2	Randomized open-label trial of cabazitaxel vs abiraterone or enzalutamide in mCRPC patients with poor-prognosis features who have not previously received abiraterone or enzalutamide	PSA response rate and/or radiographic response	From whole-blood RNA; mRNA-based, PAXgene (PreAnalytiX, Hombrechtikon, Switzerland)	NCT02254785
Abiraterone, enzalutamide, taxanes *[PCF 00056936]*	Phase 2	Prospective observational study in mCRPC patients starting standard-of-care abiraterone or enzalutamide, with potential switch to taxane chemotherapy upon progression, evaluating mechanisms of resistance related to AR-V7 and other biomarkers. Three AR-V7 assays will be compared.	PFS, OS	(1) From CTCs; mRNA-based, AdnaTest (Qiagen) (2) From CTCs; mRNA-based, RosetteSep (StemCell Technologies, Vancouver, BC, Canada) (3) From CTCs; protein-based, Epic Sciences	NCT02269982
Abiraterone, enzalutamide *[GUTG-001]*	Phase 2	Randomized open-label sequencing study of abiraterone→ enzalutamide vs enzalutamide→ abiraterone in mCRPC	PSA response rate	From whole-blood RNA; mRNA-based, PAXgene (PreAnalytiX)	NCT02125357
Abiraterone, enzalutamide *[BARRIER-P]*	Phase 2	Open-label trial of standard-of-care enzalutamide or abiraterone for mCRPC, evaluating biomarkers of response and resistance including AR-V7	PSA response rate, PSA progression	From whole-blood RNA; mRNA-based, PAXgene (PreAnalytiX)	NCT02429193

Abbreviations: AR-V7, androgen receptor splice variant 7; CTC, circulating tumor cell; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival.

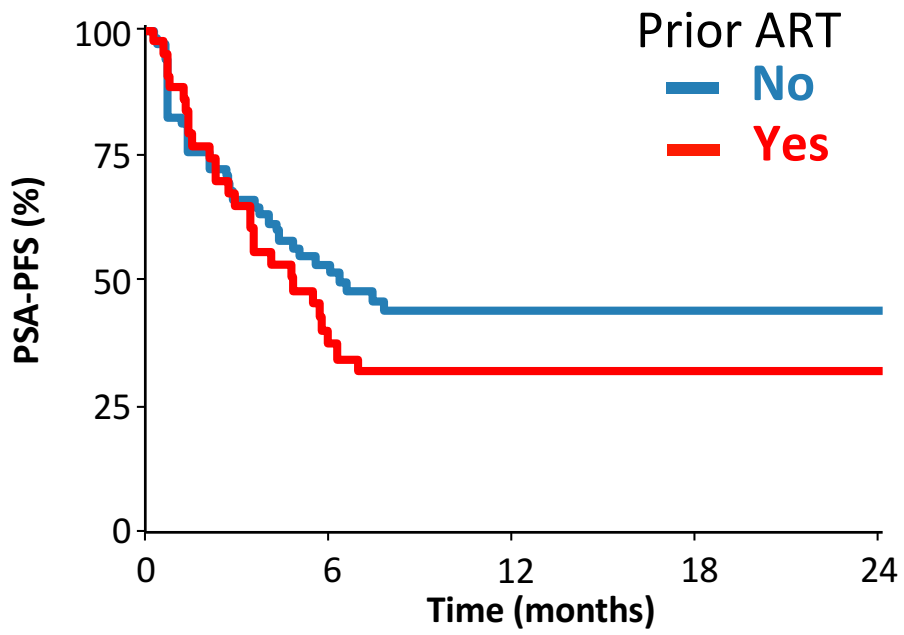
Selected therapeutic trials using agents with potential activity against AR-V7-expressing CRPC

Investigational agents	Trial phase	Description	Key outcomes	Biomarker platform	NCT number
Galeterone vs enzalutamide *[ARM0R3-SV]*	Phase 3	Randomized open-label trial of enzalutamide vs galeterone in treatment-naive AR-V7-positive mCRPC patients	rPFS, OS	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02438007
EPI-506 (AR-NTD inhibitor) *[EPI-506-CS-000I]*	Phase 1/2	Single-arm trial in men with mCRPC after progression on enzalutamide or abiraterone (one prior taxane also permitted)	Safety, PSA response rate	From CTCs; protein-based, Epic Sciences	NCT02606123
Niclosamide+enzalutamide *[NCI-2015-01246]*	Phase 1	Open-label trial of niclosamide plus enzalutamide in AR-V7-positive abiraterone-refractory mCRPC	Safety, PSA response rate	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02532114
High-dose testosterone *[RESTORE]*	Phase 2	Single-arm trial of high-dose testosterone for abiraterone- or enzalutamide-refractory mCRPC	PSA response rate, safety	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02090114
High-dose testosterone vs enzalutamide *[TRANSFORMER]*	Phase 3	Randomized study of high-dose testosterone vs enzalutamide for abiraterone-refractory mCRPC	rPFS	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02286921
Cabazitaxel *[CARVE]*	Phase 2	Single-arm open-label trial of cabazitaxel in mCRPC patients with AR-V7-positive CTCs who have previously received docetaxel	PSA response rate	From CTCs; mRNA-based, CellSearch (Janssen, Horsham, PA, USA)	NCT02621190
GSK525762 (BET inhibitor) *[GSK-115521]*	Phase 1	Open-label trial of GSK525762 in solid tumors, including CRPC	Safety, response rate	No AR-V7 testing	NCT01587703
GS-5829 (BET inhibitor) [GS-US-350-1604]	Phase 1/2	Open-label trial of GS-5829 specifically for mCRPC, used alone (phase 1) and in combination with enzalutamide (phase 2)	Safety (phase 1); PFS at 24 weeks (phase 2)	From CTCs; protein-based, Epic Sciences	NCT02607228
Ipilimumab+nivolumab *[STARVE-PC]*	Phase 2	Single-arm trial of ipilimumab plus nivolumab in AR-V7-positive mCRPC	PSA response rate, safety	From CTCs; mRNA-based, AdnaTest (Qiagen)	NCT02601014

Abbreviations: AR-NTD, androgen receptor N-terminal domain; BET, bromodomain extra-terminal motif; CTC, circulating tumor cell; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; rPFS, radiographic progression-free survival.

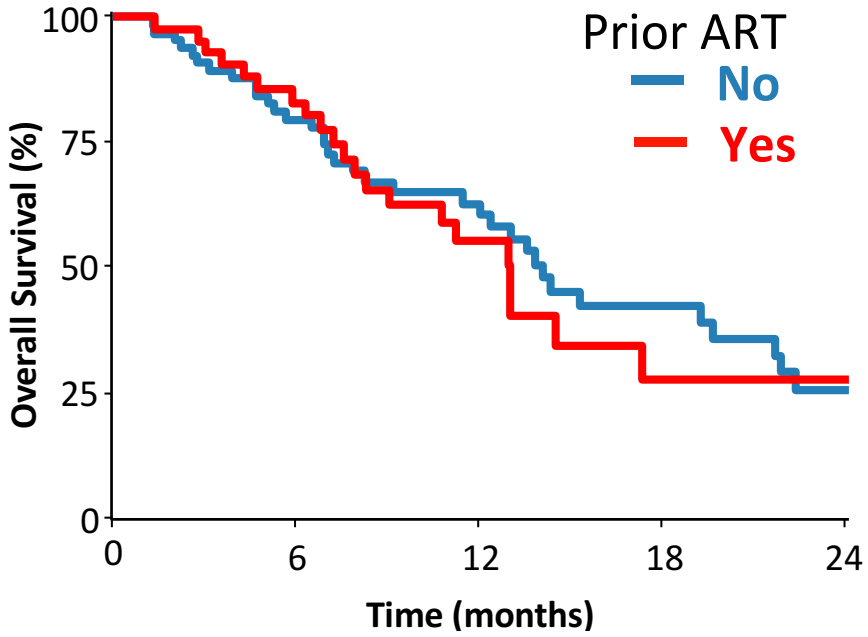
CABA May Remain Active in Patients Progressing With ART

Progression-free survival



Pts at risk					
No	70	31	14	9	6
Yes	44	14	7	2	0

Overall survival

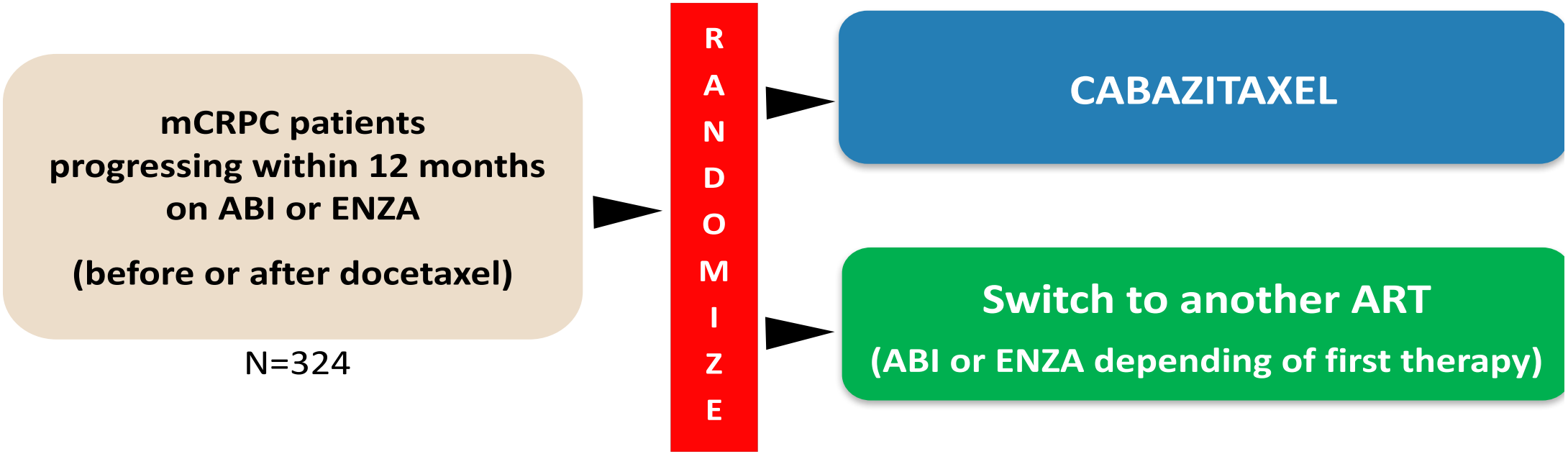


Pts at risk					
No	70	48	26	13	6
Yes	44	31	14	2	1

Prospective, randomized phase 2 study of cabazitaxel ± budesonide

Van Soest RJ et al. Eur J Cancer. 2015;51:2562-9.

CARD Study



Stratification factors: ECOG PS (0/1 vs 2), time to progression (≤6 vs 6-12 mos), timing of ART (before vs after DOC)

Primary endpoint: radiographic PFS

Secondary endpoints: PSA response, ECOG PS, PFS (clinical or radiological), objective tumor response, pain, QoL, time to SSEs, OS, safety biomarkers

NCT02485691. https://clinicaltrials.gov/

Novel compounds in clinical trials for treatment of CRPC with suggested mechanisms targeting the AR and/or its constitutively active variants.[a]

Compound	Suggested mechanism
ODM-201	• AR antagonist, inhibiting nuclear translocation of AR including *T878A*, *W742L*, *F877L* mutants
EPI-506	• AR antagonist binding the AR NTD
Galeterone	• Inhibits CYP17 • AR antagonist • Induces proteasomal degradation of AR and AR variants
Niclosamide	• Inhibits AR-V7 transcriptional activity • Promotes AR-V7 proteasomal degradation
JQ1, OTX015	• Bromodomain and extra-terminal (BET) inhibitors disrupting interactions between AR NTD, co-factors and chromatin, inhibiting transcriptional activity
Onalespib	• HSP90 inhibitor blocking AR-V7 mRNA splicing
EZN-4176, AZD-5312	• Antisense oligonucleotides (ASOs) targeting expression of AR and AR variants

International Journal of Urology (2016) 23, 654–665 doi: 10.1111/iju.13137

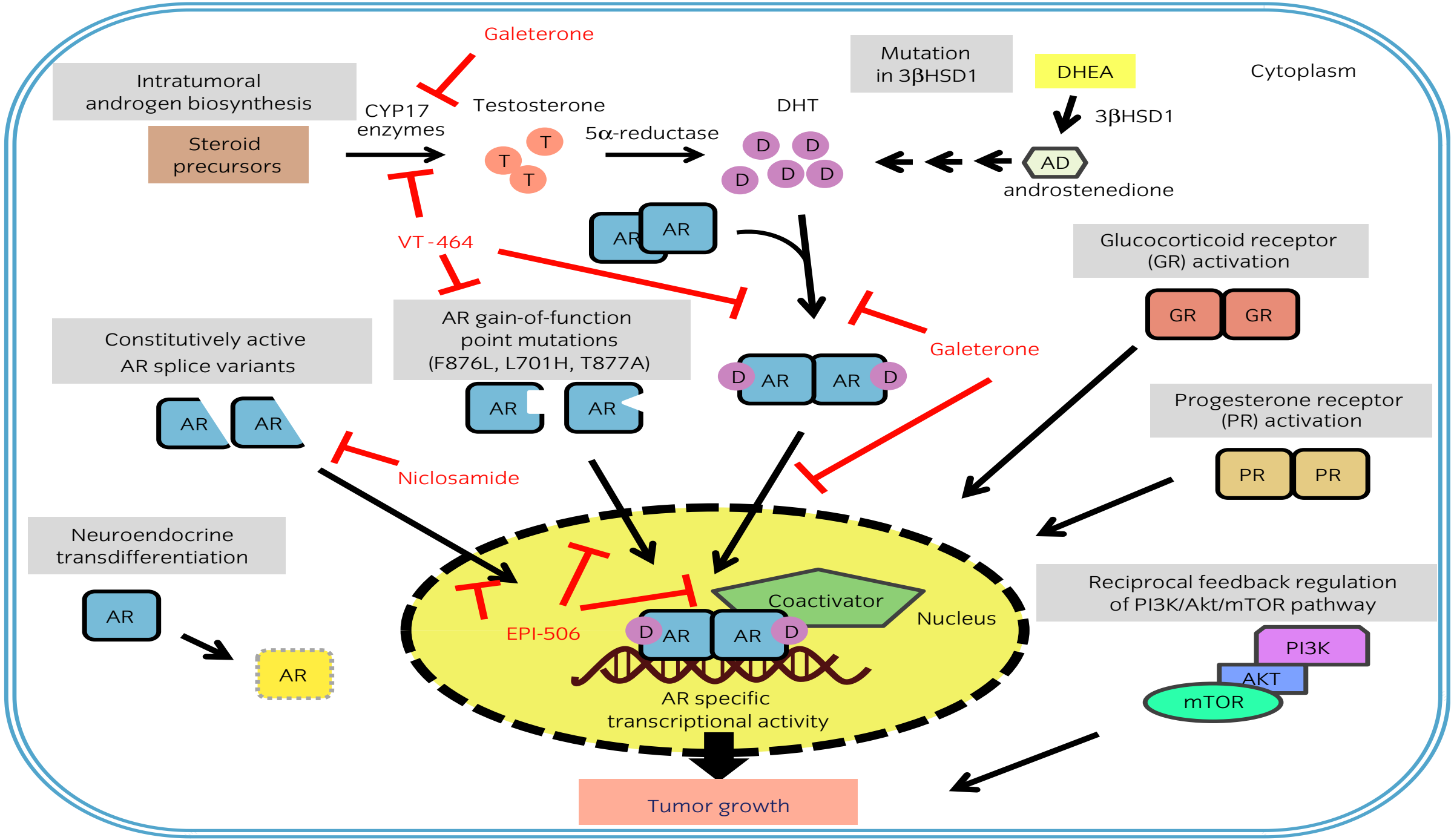
Review Article

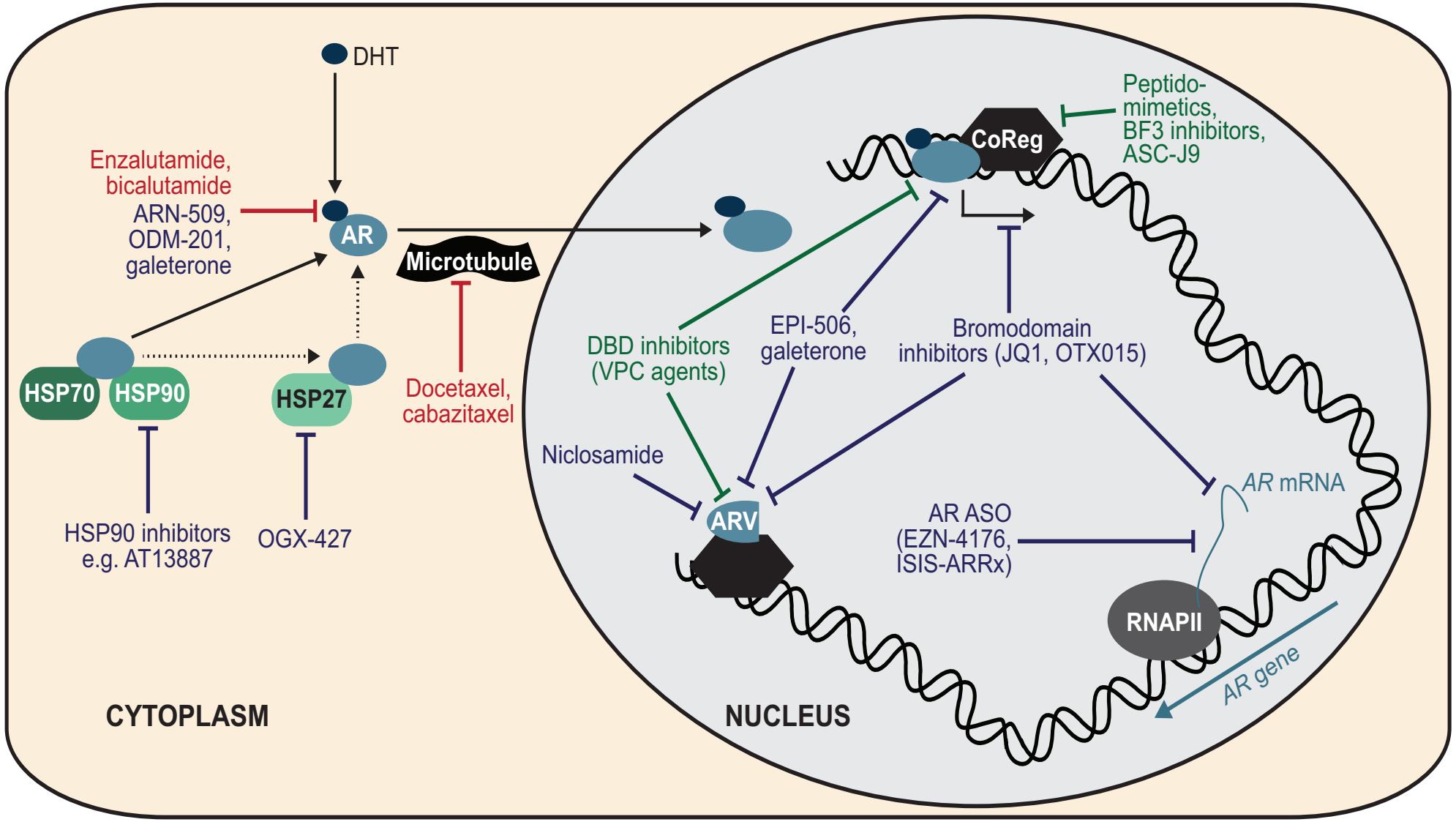
Androgen receptor targeted therapies in castration-resistant prostate cancer: Bench to clinic

Yusuke Imamura and Marianne D Sadar
Genome Sciences Center, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

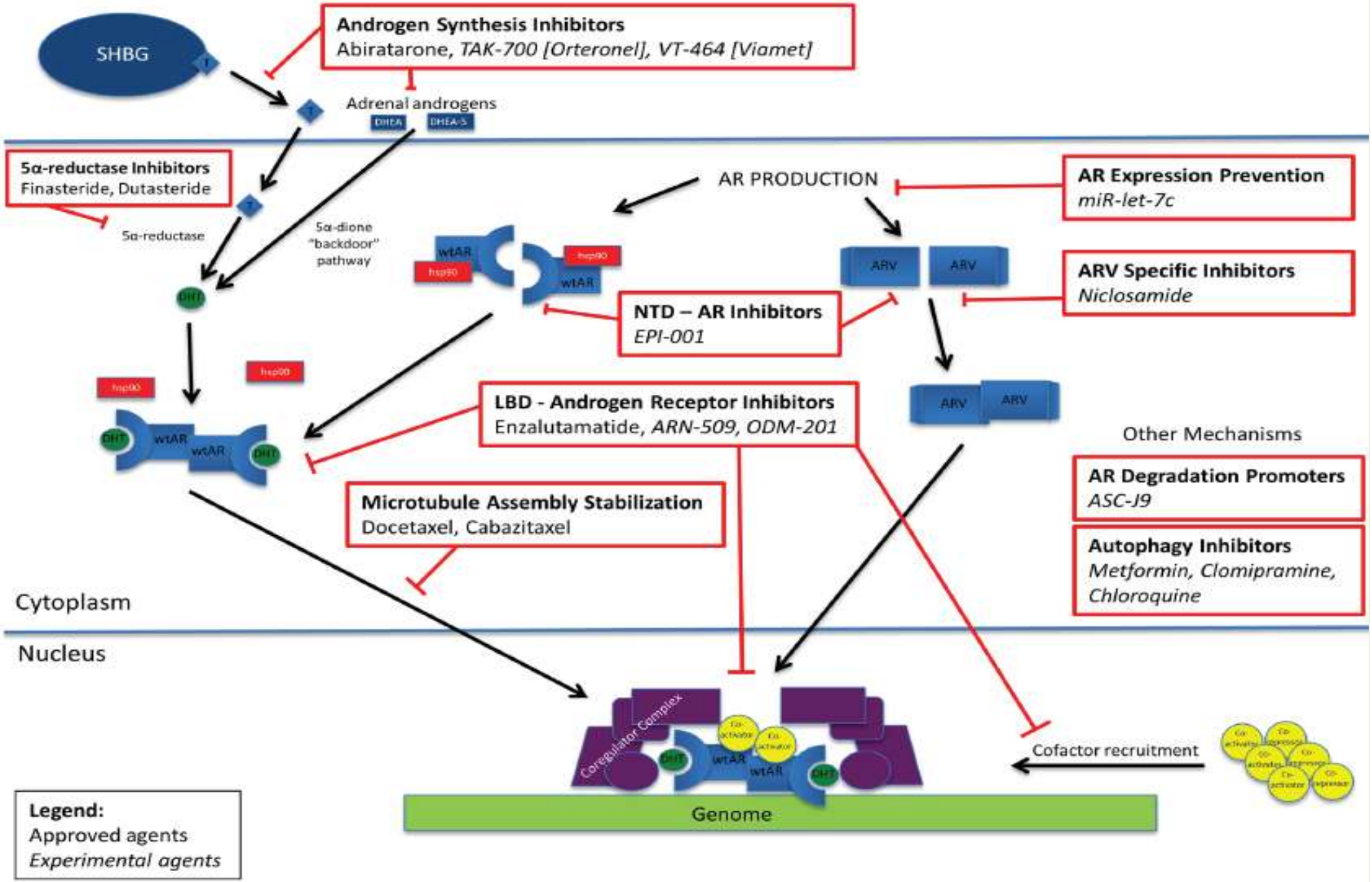
Table 1 Novel AR targeted drugs in clinical trials

Agents	Mechanism	Advantage	Target	Clinical study ID	Phase
Apalutamide (ARN-509)	AR antagonist (AR-LBD)	High affinity, less blood–brain barrier penetration	Non-mCRPC patients	NCT01946204	3
ODM-201 (BAY-1841788)	AR antagonist (AR-LBD)	High affinity, does not cross blood–brain barrier	High-risk non-mCRPC patients	NCT02200614	3
Seviteronel (VT-464)	CYP17 inhibitor (17,20-lyase selective inhibition)	Does not need corticosteroid	CRPC patients progressing on enzalutamide or abiraterone	NCT02445976	2
			CRPC patients	NCT02361086	1/2
			CRPC patients	NCT02012920	1/2
			CRPC patients previously treated with enzalutamide	NCT02130700	2
Galeterone	CYP17A1 inhibitor (17,20-lyase selective inhibition), AR antagonist, AR degrader	Does not need corticosteroid	mCRPC patients positive for AR-V7	NCT02438007	3
			CRPC patients	NCT01709734	2
Niclosamide	Proteasome-dependent AR degrader (inhibit AR-V7)	Enhances response to enzalutamide	mCRPC patients who are AR-Vs positive	NCT02532114	1
EPI-506	AR antagonist (AR-NTD, AF-1)	Targets FL-AR and AR-Vs	mCRPC patients who failed enzalutamide or abiraterone	NCT02606123	1/2


Galeterone
Intratumoral androgen biosynthesis
Steroid precursors
CYP17 enzymes
Testosterone
5α-reductase
DHT
Mutation in 3βHSD1
DHEA
3βHSD1
AD
androstenedione
Cytoplasm
VT-464
AR
AR
Glucocorticoid receptor (GR) activation
GR
GR
Constitutively active AR splice variants
AR gain-of-function point mutations (F876L, L701H, T877A)
D
AR
AR
D
Galeterone
Progesterone receptor (PR) activation
PR
PR
Niclosamide
Neuroendocrine transdifferentiation
EPI-506
Coactivator
Nucleus
Reciprocal feedback regulation of PI3K/Akt/mTOR pathway
PI3K
AKT
mTOR
AR specific transcriptional activity
Tumor growth



Novel strategies to target persistent androgen receptor signaling in CRPC. Recently approved agents are shown in red; agents in clinical trials are shown in blue; novel agents still in pre-clinical development are shown in green. CoReg, coregulator; HSP, heat shock protein.


SHBG
Androgen Synthesis Inhibitors
Abiratarone, TAK-700 [Orteronel], VT-464 [Viamet]
Adrenal androgens
DHEA
DHEA-S
5α-reductase Inhibitors
Finasteride, Dutasteride
5α-reductase
5α-dione "backdoor" pathway
AR PRODUCTION
AR Expression Prevention
miR-let-7c
ARV Specific Inhibitors
Niclosamide
NTD – AR Inhibitors
EPI-001
LBD - Androgen Receptor Inhibitors
Enzalutamatide, ARN-509, ODM-201
Microtubule Assembly Stabilization
Docetaxel, Cabazitaxel
Other Mechanisms
AR Degradation Promoters
ASC-J9
Autophagy Inhibitors
Metformin, Clomipramine, Chloroquine
Cytoplasm
Nucleus
Coregulator Complex
Cofactor recruitment
Genome
Legend:
Approved agents
Experimental agents

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 2), pp: 3724-3745

Review

Androgen receptor-dependent and -independent mechanisms driving prostate cancer progression: Opportunities for therapeutic targeting from multiple angles

David T. Hoang[1], Kenneth A. Iczkowski[2], Deepak Kilari[3], William See[4], Marja T. Nevalainen[2,5]

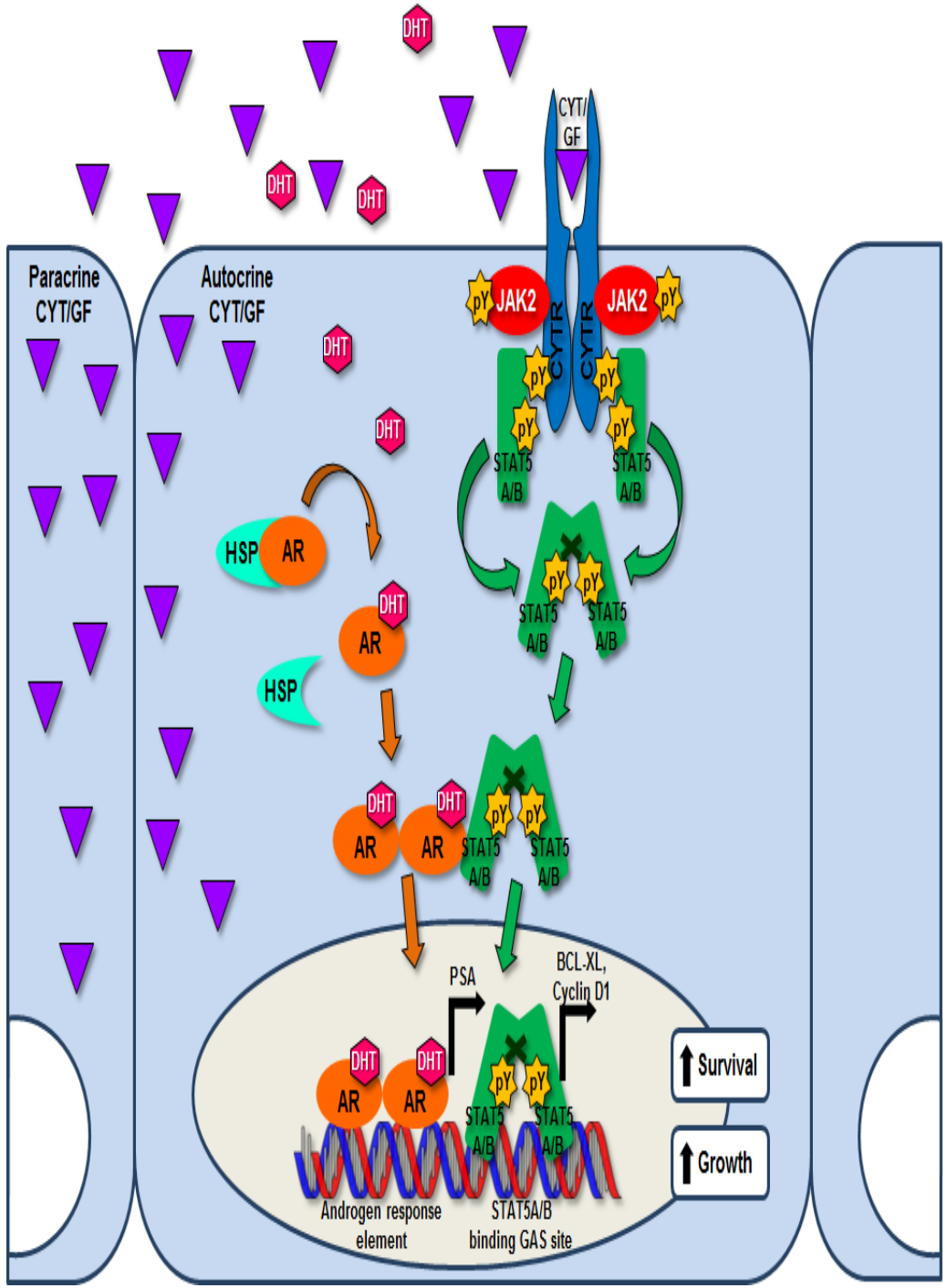
Therapeutic targeting of Stat5a/b may represent a **dual strategy** to inhibit growth and viability of prostate cancer.

AR-dependent functions:

Stat5a/b protection of AR liganded by antiandrogens from degradation and enhancement of AR signaling.

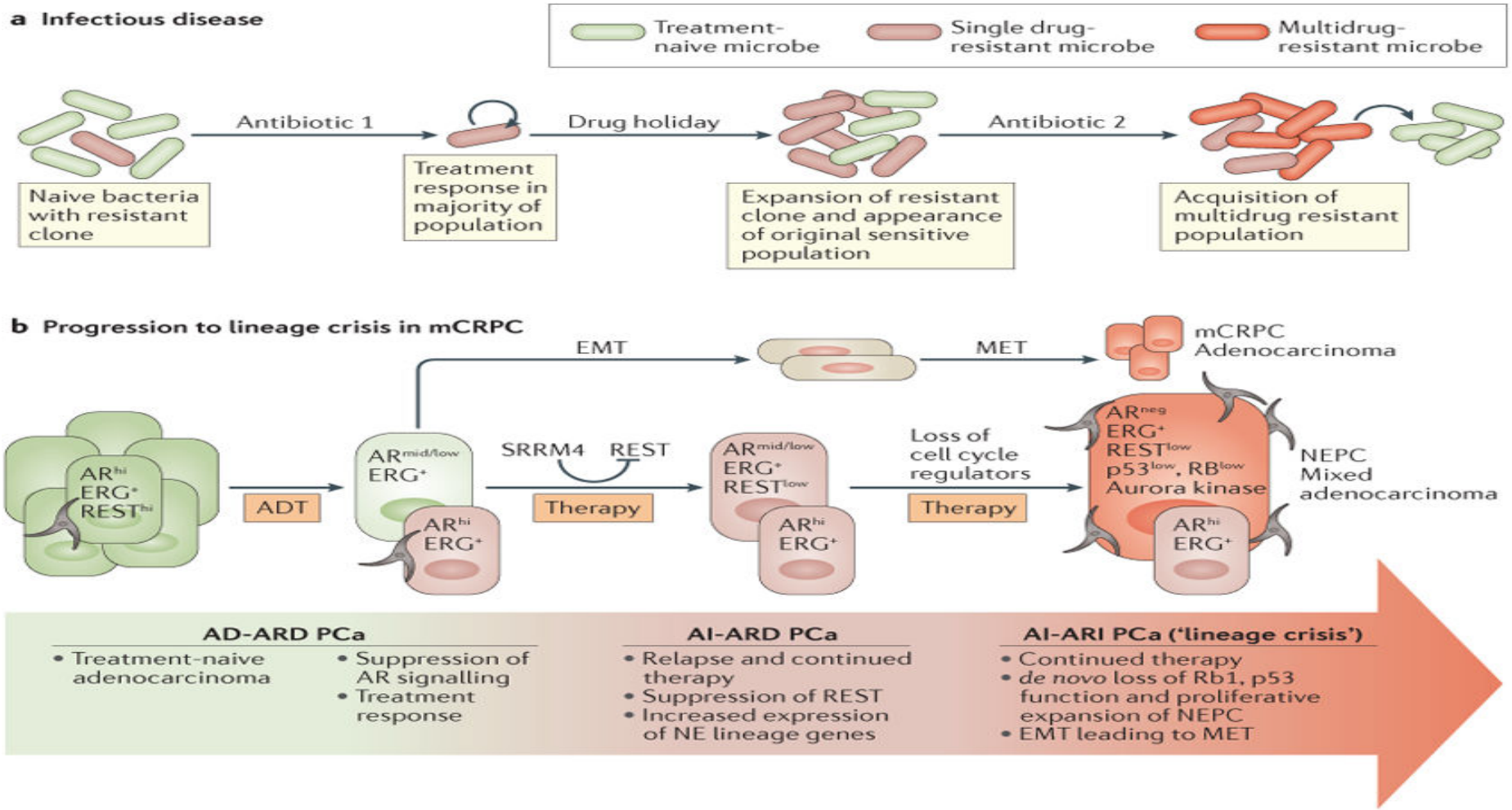
AR-independent functions:

Stat5a/b induction of Stat5a/b-regulated proliferation and survival genes independently of AR.



Proposed strategies to overcome abiraterone and/or enzalutamide mechanism of resistance and ongoing clinical trial.

Mechanism of resistance	How to overcome it	Ongoing clinical trials
• AR overexpression • Androgen biosynthesis pathway upregulation • Intracrine androgen synthesis	Enzalutamide in combination with abiraterone acetate	NCT01650194: Phase 2
	Increased-dose abiraterone acetate (2000 mg daily)	NCT01637402: Phase 2
	ARN-509 + abiraterone	NCT02123758: Phase 1
	ARN-509 + abiraterone	NCT01792687: Phase 1
	ARN-509 + abiraterone	NCT02257736: Phase 3
	Galeterone (AR antagonist and CYP17A1 inhibitor)	NCT01709734: Phase 2
	Onapristone (progesterone receptor inhibitor)	NCT02049190: Phase1/2
• Immune evasion	Pembrolizumab (anti PD-1) following Enzalutamide	NCT02312557: Phase 2
	PROSTVAC (vaccine therapy) + enzalutamide	NCT01867333
• ARVs	EPI-506 (NTD-binding AR antagonist)	NCT: Pending FDA approval
• Autophagy	OGX-427 + abiraterone	NCT01681433: Phase 2
	Alisertib (selective aurora A kinase induction	NCT01848067: Phase 1/2
	inhibitor) + abiraterone	Phase 1/2
	AT 13387 (HSP90 inhibitor) + abiraterone	NCT01685268: Phase 1/2
• Activation of other pathways	Crizotinib + enzalutamide	NCT02207504: Phase 1
	Abiraterone + BEZ235 (Pi3K and mTOR inhibitor) or Abiraterone + BKM120 (Pi3K inhibitor)	NCT01634061: Phase 1
	Dovitinib (multitargeted TKI) + Abiraterone	NCT01994590: Phase 2
	Dasatibib (mutitargeted TKI) + abiraterone	NCT01685125: Phase 2
	Olaparib (PARP-inhibitor) + abiraterone	NCT01972217: Phase 2
	Everolimus (m-TOR inhibitor) + ARN-509 (AR antagonist)	NCT02106507: Phase 1
	BI 836845 (anti IGF1/IGF2) + enzalutamide	NCT02204072: Phase 1
	Cabozantinib (anti c-MET and anti VEGFR2) + abiraterone	NCT01574937: Phase 1
• Other mechanisms	Metformin + abiraterone	NCT01677897: Phase 2
	Metformin + enzalutamide	NCT02339168: Phase 1
	Cabazitaxel + abiraterone	NCT02218606: Phase 2



Nat Rev Clin Oncol. 2017 May ; 14(5): 269–283. doi:10.1038/nrclinonc.2016.181.

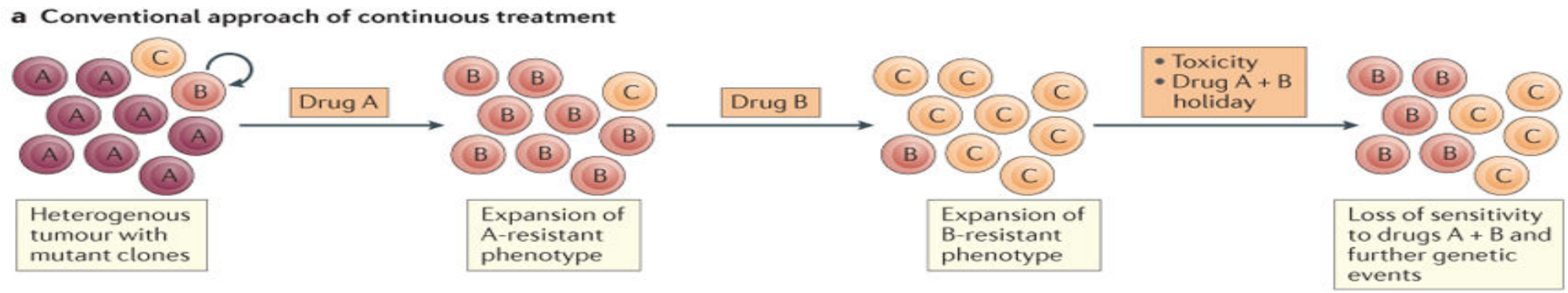
Strategies to avoid treatment-induced lineage crisis in advanced prostate cancer

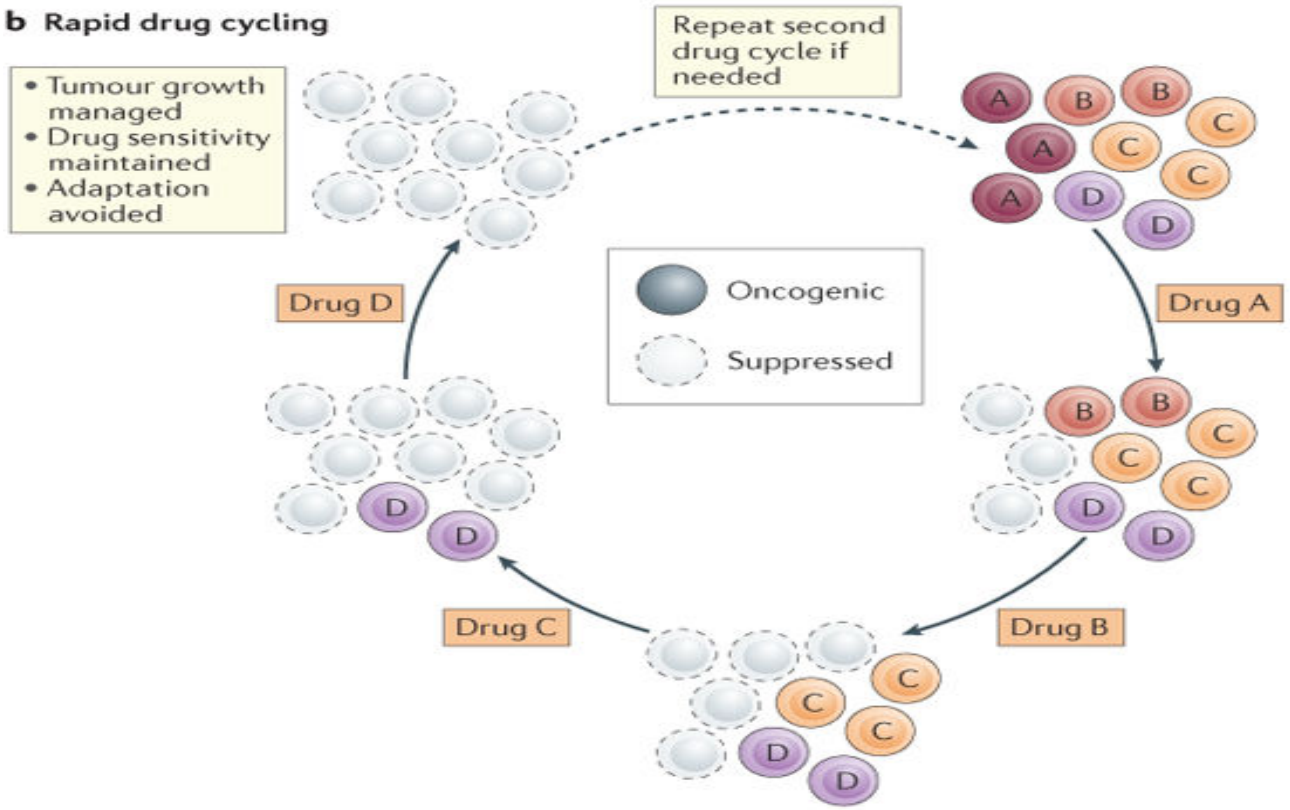
Guilhem Roubaud[1], **Bobby C. Liaw**[2], **William K. Oh**[2], and **David J. Mulholland**[2]

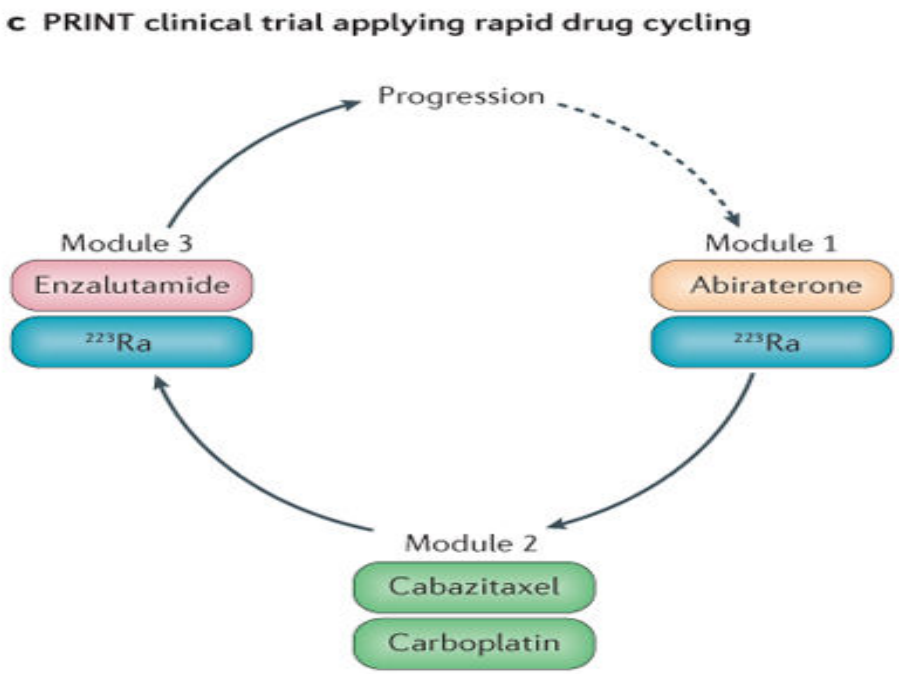
[1]Department of Medical Oncology, Institut Bergonié, 229 Cours de l'Argonne, Bordeaux 33076, France

[2]Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, 1470 Madison Avenue, New York, New York 10029, USA

PROSTATE CANCER INTENSIVE NON-CROSS REACTIVE (PRINT)





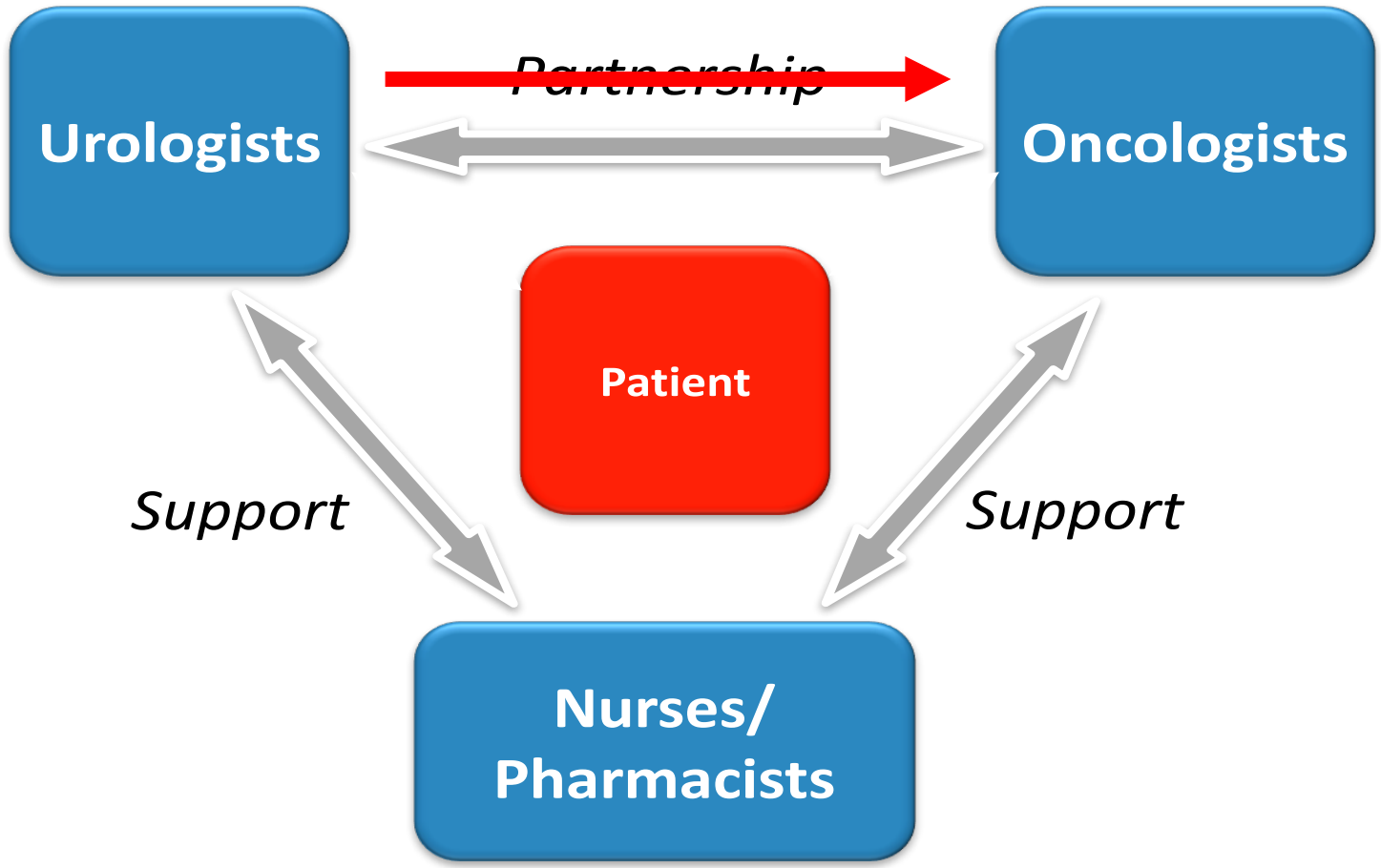


The Challenge for the Uro-oncologist in mCRPC

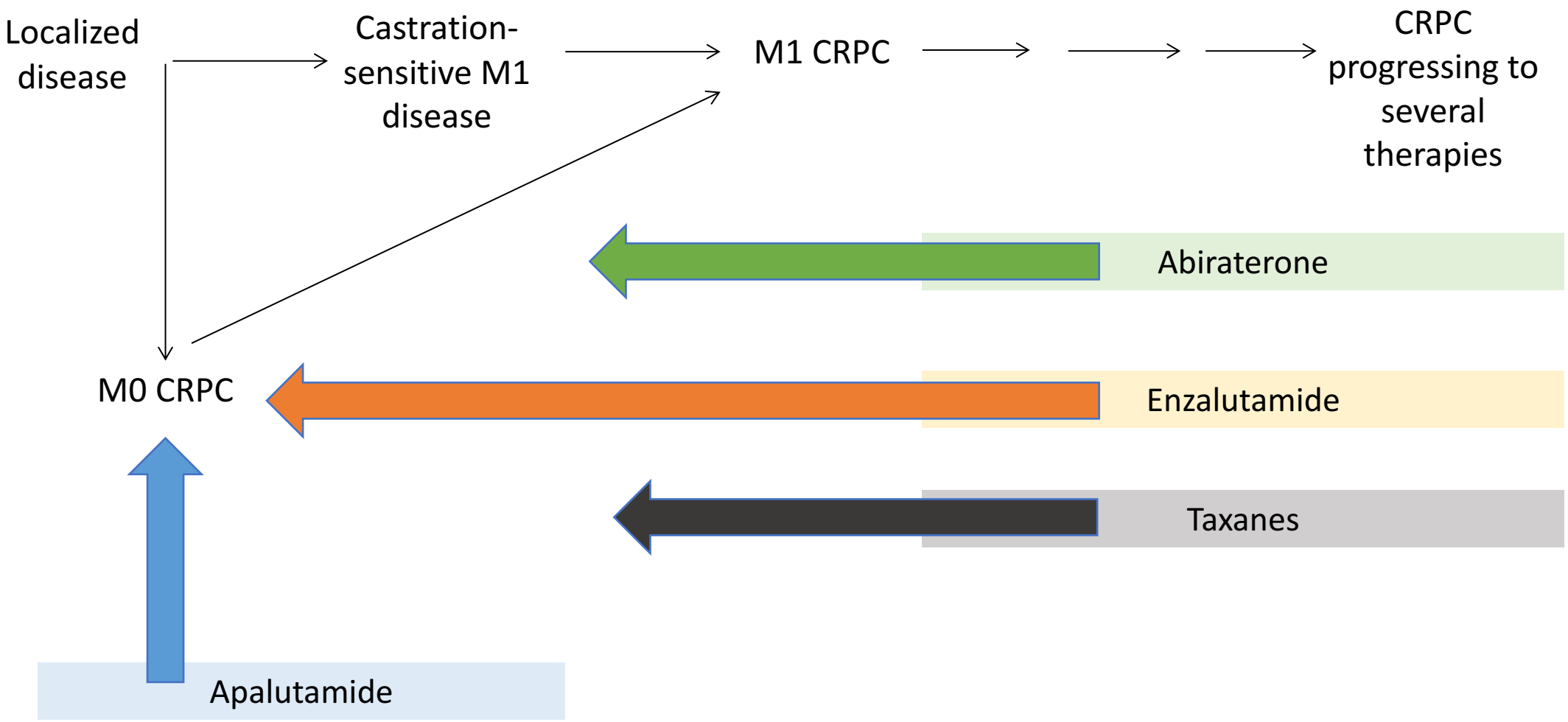
"Urólogos y RT"

- **To identify mCRPC patients with poor response to ENZA or ABI**
  … and to offer them first-line chemotherapy
- **To identify disease progression on 1L therapy at an early time point**
  … and to offer subsequent therapy before performance status deteriorates
- **To pro-actively manage adverse events of new treatment options**
  … to optimize treatment outcomes (quality of life, survival)
- **Multidisciplinary care a key to success!!**

Patient Management: A Patient-Centered Partnership



We Need Biomarkers of AR Signaling Readout



By changing treatment paradigm, we are forcing tumor evolution

My Personal View and Hope

‘All eligible patients should be offered the benefits of all proven and effective treatments to…

MAXIMIZE SURVIVAL WITH PRESERVED/IMPROVED QUALITY OF LIFE’