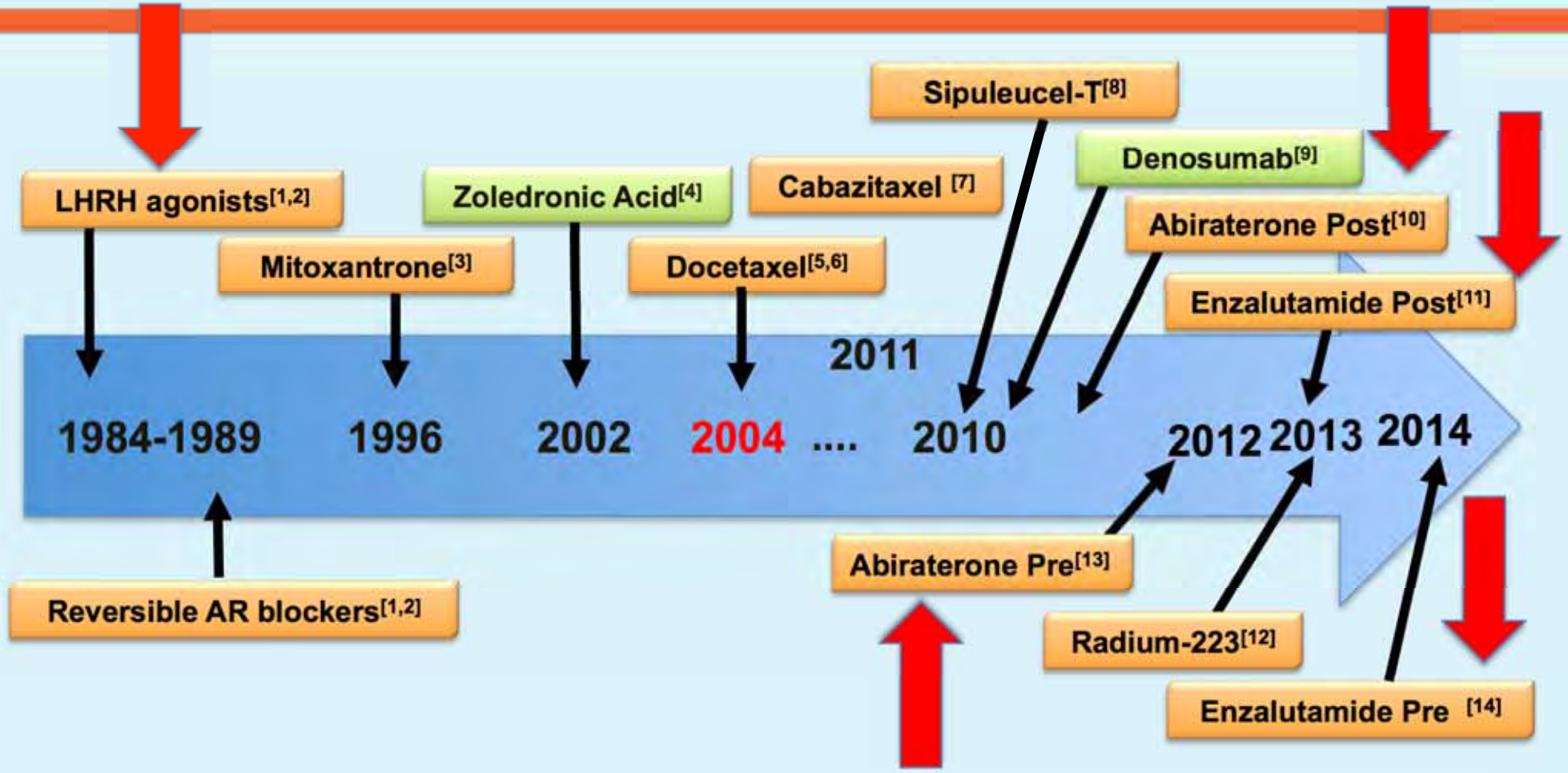
Hormonal Therapy In the Setting of CRPC

Leonard G. Gomella, MD
Chairman
Department of Urology
Sidney Kimmel Cancer Center
Philadelphia, PA

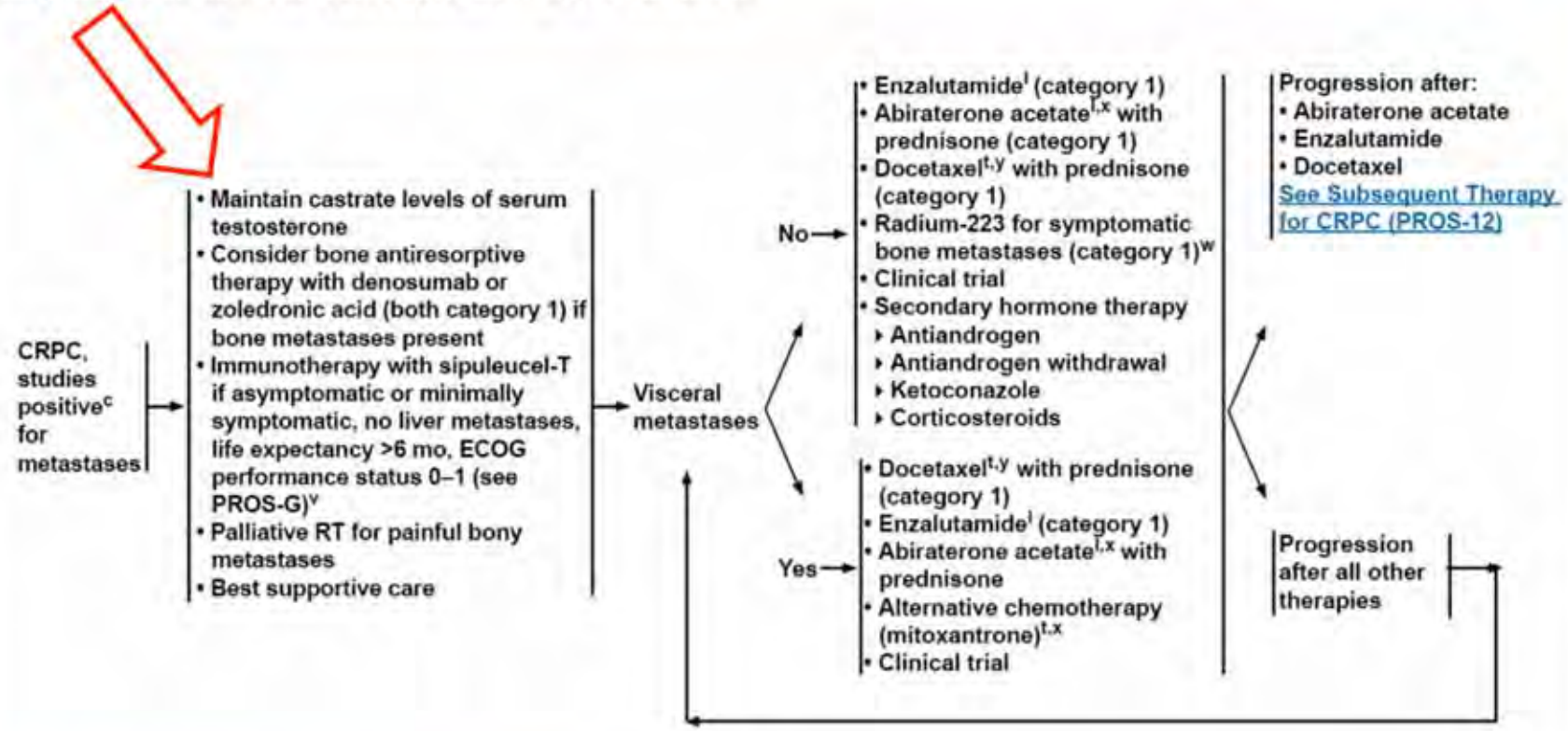
Jefferson
HEALTH IS ALL WE DO

Before 2010, the last agent approved for the treatment of CRPC was docetaxel



1. The Leuprolide Study Group. NEJM 1984;311:1281-1286. 2. Crawford ED, et al. NEJM. 1989;321:419-424. 3. Tannock IF, et al. J Clin Oncol. 1996;14:1756-1764. 4. Saad F, et al. JNCI 2002;94:1458-1468. 5. Petrylak DP, et al. NEJM. 2004;351:1513-1520. 6. Tannock IF, et al. NEJM. 2004;351:1502-1512. 7. de Bono JS, et al. Lancet. 2010;376:1147-1154. 8. Kantoff PW, et al. NEJM. 2010;363:411-422. 9. Fizazi K, et al. Lancet. 2011;377:813-822. 10. de Bono JS, et al. NEJM. 2011;364:1995-2005. 11. Scher HI, et al. NEJM. 2012 Sep 27;367(13):1187-97. 12. Parker et al. *NEJM*. 2013;369:213-223.13. Beer T et al. 2014 ASCO GU San Francisco, CA 14. Beer T NEJM 2014; 371:424-433

ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC



[c] See Principles of Imaging (PROS-B).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[v] Sipuleucel-T has not been studied in patients with visceral metastases.
[w] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
[x] For patients who are not candidates for docetaxel-based regimens.
[y] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Castration-Resistant Prostate Cancer (CRPC)

New Definition: 2 consecutive rises in PSA while on ADT and serum T <50 ng/mL

- Check serum T periodically on ADT

"Androgen resistant", "androgen independent", "hormone refractory" terms longer used

- Prostate cancer in CRPC maintains response to hormonal axis

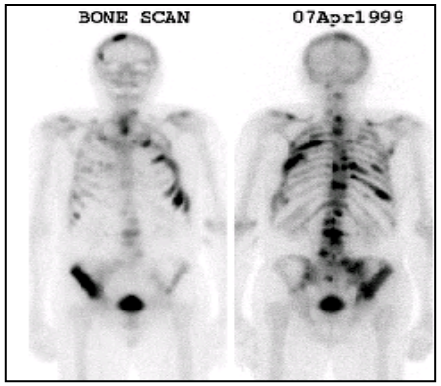
Do people who have a lower T with ADT do better?

- Some data suggests yes

LHRH agonists, antagonists or surgical castration do not ablate T to the lowest levels possible

ADT, androgen deprivation therapy; T, testosterone; LHRH, luteinizing hormone- releasing hormone

Treatment of Metastatic PC



Androgen Deprivation
+/- AR antagonists

↓ *Cell Cycle Arrest/Death (40/60%)*

Remission

↓ ***12-36 months***

Relapse

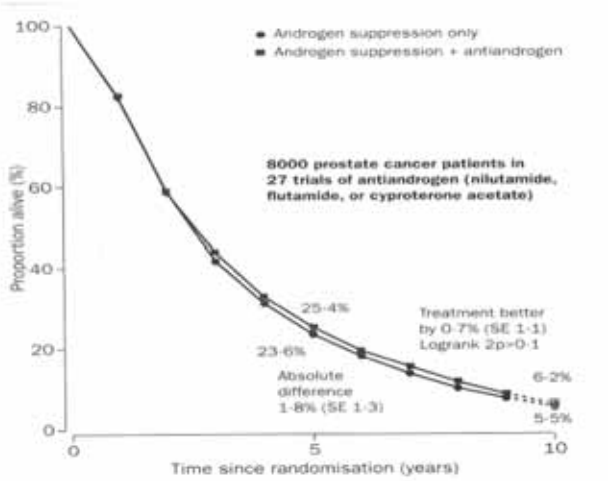
Cell Cycle resumes

"Castration Resistant" (CRPC)

↓

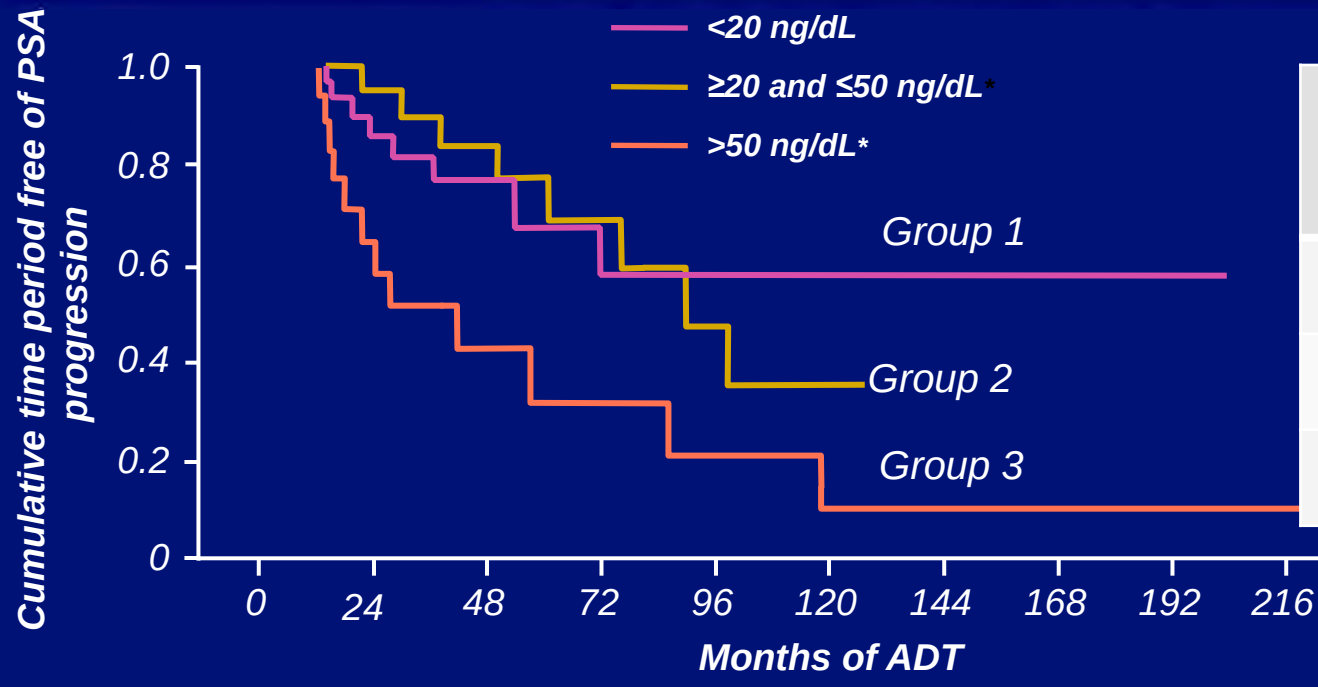
ors that re-activate androgen pathways

Castration +/- Antiandrogen



ormone Naïve Disease- Importance of Lower T Levels: A Hypothesis-Generati Analysis From a Retrospective Study

Retrospective analysis of 73 patients with nonmetastatic prostate cancer who received 3-month depot of LHRH agonist



	Mean Time Free of Androgen-Independent Progression
Group 1	106 months
Group 2	90 months
Group 3	72 months

Patients with testosterone levels <32 ng/dL had an average of an additional 4 years until castrate-resistant progression

*Morote J. J Urol. 2007;178:1290.

Secondary “Hormonal” Therapy:

Responses Rarely Durable

Type of Therapy	Response Rate
Steroids	**10%-20%**
Ketoconazole	**30%-60%**
Estrogens	**40%-60%**
Anti-androgens	**20%**
Anti-androgen Withdrawal	**20% rarely durable**

in Genitourin Cancer. 2011 Dec;9(2):95-103Curr Oncol. 2010 Sept; 17(Supplement 2): S72–S79

CRPC Maintains Sensitivity to Low Levels of Androgens

- Androgen biosynthesis from adrenal precursors and De novo synthesis
- Cells become hypersensitive to small amounts of androgen through alterations in the androgen receptor (AR), including
  - Increase in the expression of ARs
  - Mutations in the AR structure
  - Activation of the AR independent of androgens

Reducing androgens to lowest levels possible is desirable in CRPC

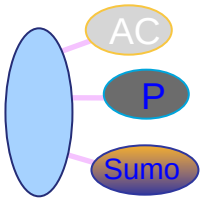
1. Chen CD *et al. Nature Med* 2004;10:33–39.
2. Taplin ME *et al. J Clin Oncol* 2003;21:2673–2678.
3. Pienta KJ *et al. Clin Cancer Res* 2006;12:1665–1671

CRPC Prostate Cancer: "Adapting" to castrate environment

Hormone Therapy

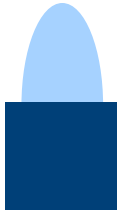
selective pressure

MUTATION
•*gain of function*



Crosstalk
AR –Sig Path

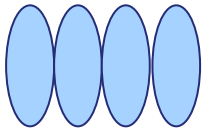
Post-translational Modifications of AR



AR SPLICE VARIANTS

COFACTOR PERTURBATION
•*CoAct gain*
•*CoR loss/dismissal*

INTRACRINE ANDROGEN SYNTHESIS



Amplification\ Overexpression AR

Alterations of Steroid Transporters

adaptation

RESTORED AR ACTIVITY
(rising PSA)

RECURRENT TUMOR DEVELOPMENT

CRPC

Penning & Knudsen 2010

New Theories for CRPC

Based on Translational Discoveries

- CaP responds to castration by synthesizing androgens f weaker androgens and/or cholesterol
- Androgen Receptor (AR) may respond to castration wit molecular and biochemical alterations that cause hypersensitivity to low levels of androgens
  - AR upregulation/mutations/promiscuous activation
- Progressing prostate cancer with low/castrate levels of testosterone is STILL sensitive to androgens

Newer CRPC "Hormonal Agents" (Androgen Biosynthesis Inhibitors/Androgen Receptor Pathway)

FDA Approved*

- Abiraterone acetate (ABI)*
- Enzalutamide (MDV3100) (ARSI)*
- TOK001 (Galeterone: ABI/ARSI/AR degradation)
- ARN 509 (ARSI)
- EPI-001 (AR N-Terminal)
- SNARE-1 (selective nuclear receptor exporter-1)

Terminated:

- TAK700 (Orteronel: ABI) (ELM-PC4 pre chemo no survival advantage)

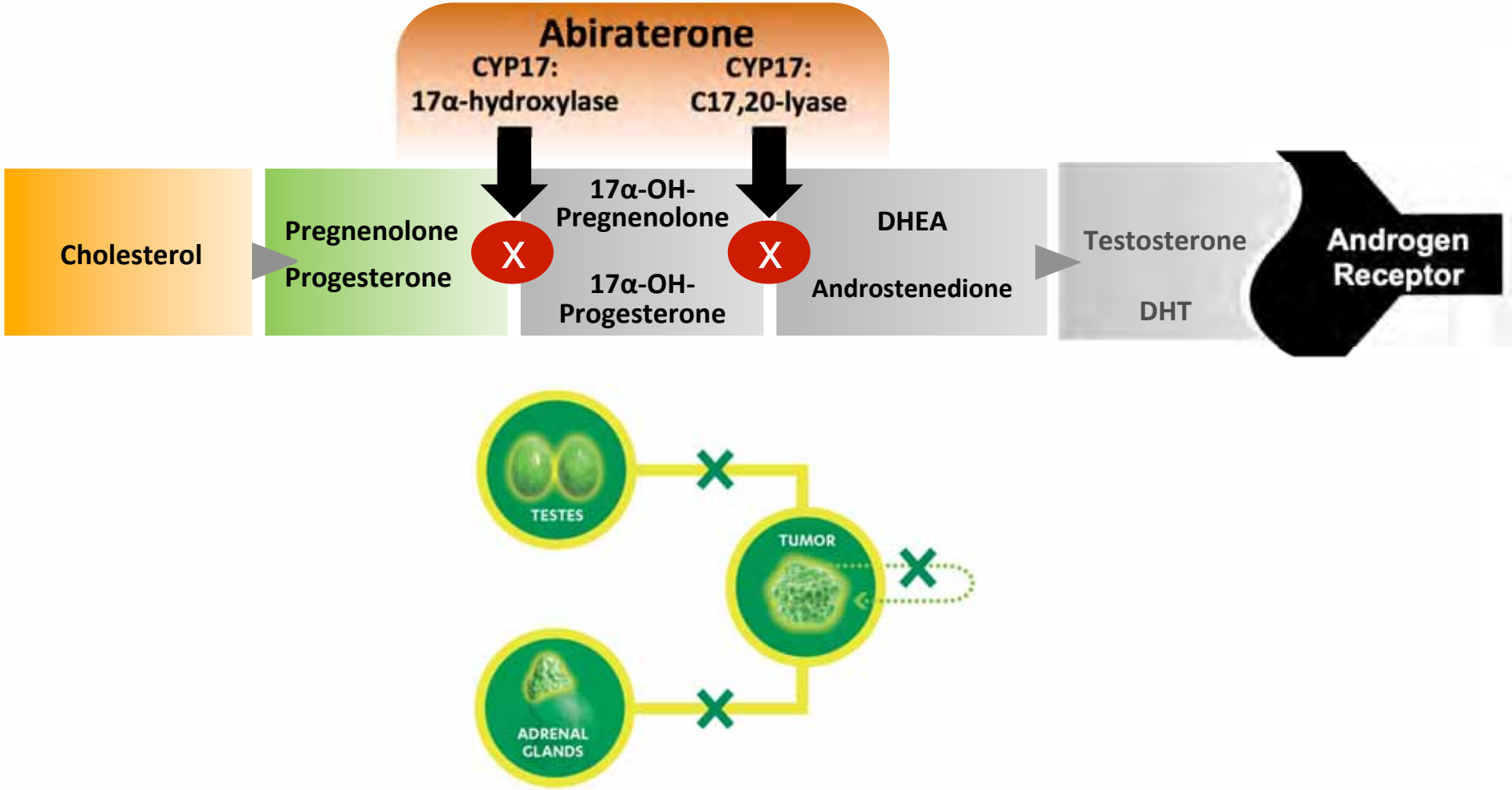
Agents with OS Benefit in mCRPC

Drug[1-3]	Trial	Comparator	Primary Endpoint	FDA Approval
Chemotherapy-naïve				
Abiraterone acetate + prednisone	COU-AA-302	Placebo + prednisone	OS benefit 5.2 months*	2012
Sipuleucel-T	IMPACT	Placebo	OS benefit 4.1 months	2010
Radium-223	ALSYMPCA	Placebo	OS benefit 3.6 months	2013
Enzalutamide	PREVAIL	Placebo	OS benefit 4 months	2014
Post-chemotherapy				
Abiraterone acetate + prednisone	COU-AA-301	Placebo + prednisone	OS benefit 4.6 months	2011
Enzalutamide	AFFIRM	Placebo	OS benefit 4.8 months	2012
Cabazitaxel + prednisone	TROPIC	Mitoxantrone + prednisone	OS benefit 2.4 months	2010
Docetaxel + prednisone	TAX327	Mitoxantrone + prednisone	OS benefit 2.4 months	2004

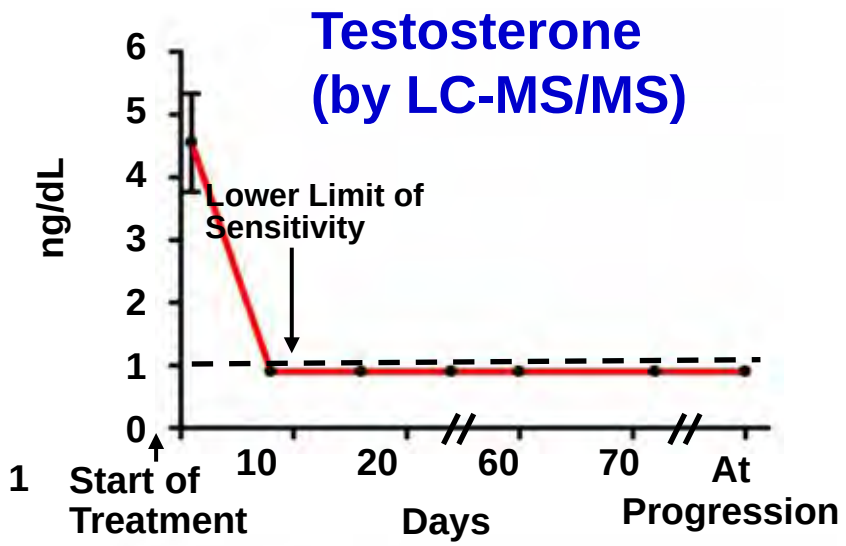
**P*=0.0151. Did not meet the prespecified value for statistical significance.

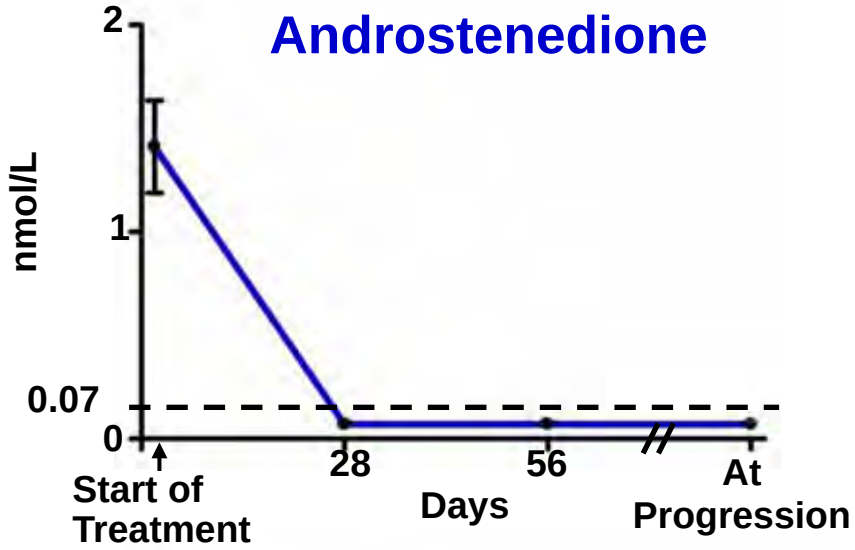
1. Ryan CJ et al. *N Engl J Med.* 2013;368:138-148. 2. El-Amm J et al. *Ther Adv Med Oncol.* 2013;5:25-40. 3. Medivation Press Release. October 2013. http://investors.medivation.com/releasedetail.cfm?ReleaseID=798880. Accessed November 4, 2013. 4. TAXOTERE [package insert]. Tombal B, et al. EAU Congress. March 20-24, 2015; Madrid, Spain.

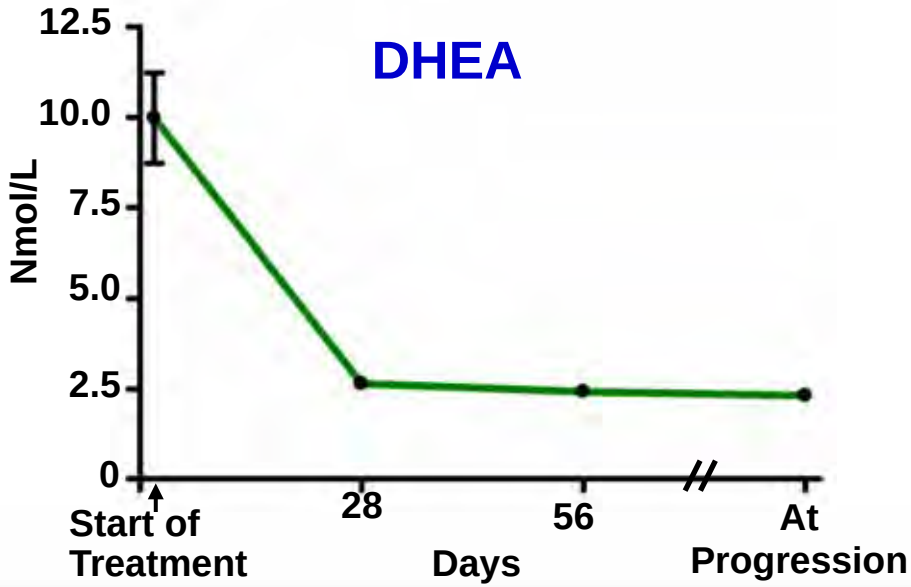
Abiraterone: Mechanism of Action

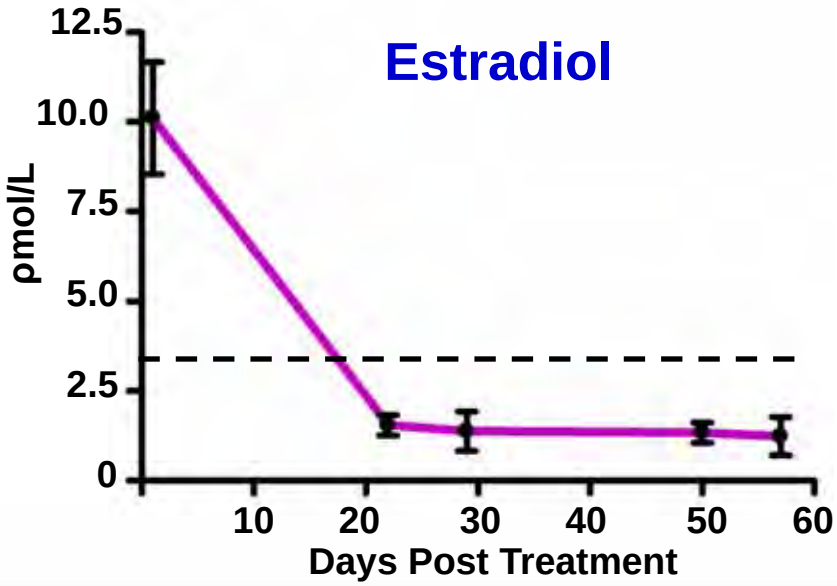


Abiraterone Suppresses Steroids Downstream of C17,20-lyase

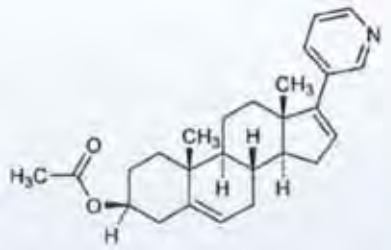








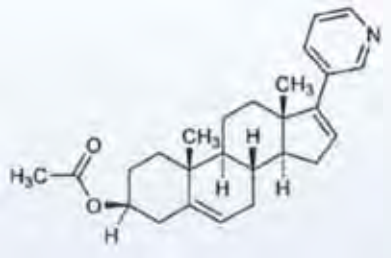
Abiraterone Administration



- Administration
  - 1,000 mg (4 , 250mg tablets) once daily on an empty stomach with prednisone 5mg BID
  - Monitor BP/LFT/potassium
- Dose Modifications
  - Dosage adjustment necessary if hepatotoxicity occurs
    - ALT/AST 5x NL or bilirubin 3x NL stop medication
    - Resume at 750mg daily once ALT/AST 2.5x NL or bilirubin 1.5x NL

J.M. Gaya, et al. *Expert Review Anticancer Therapy*. 2013:13: 819-827. ZYTIGA® (abiraterone acetate) [package insert]. Horsham, PA: Centocor Ortho Biotech Inc.; 2011.

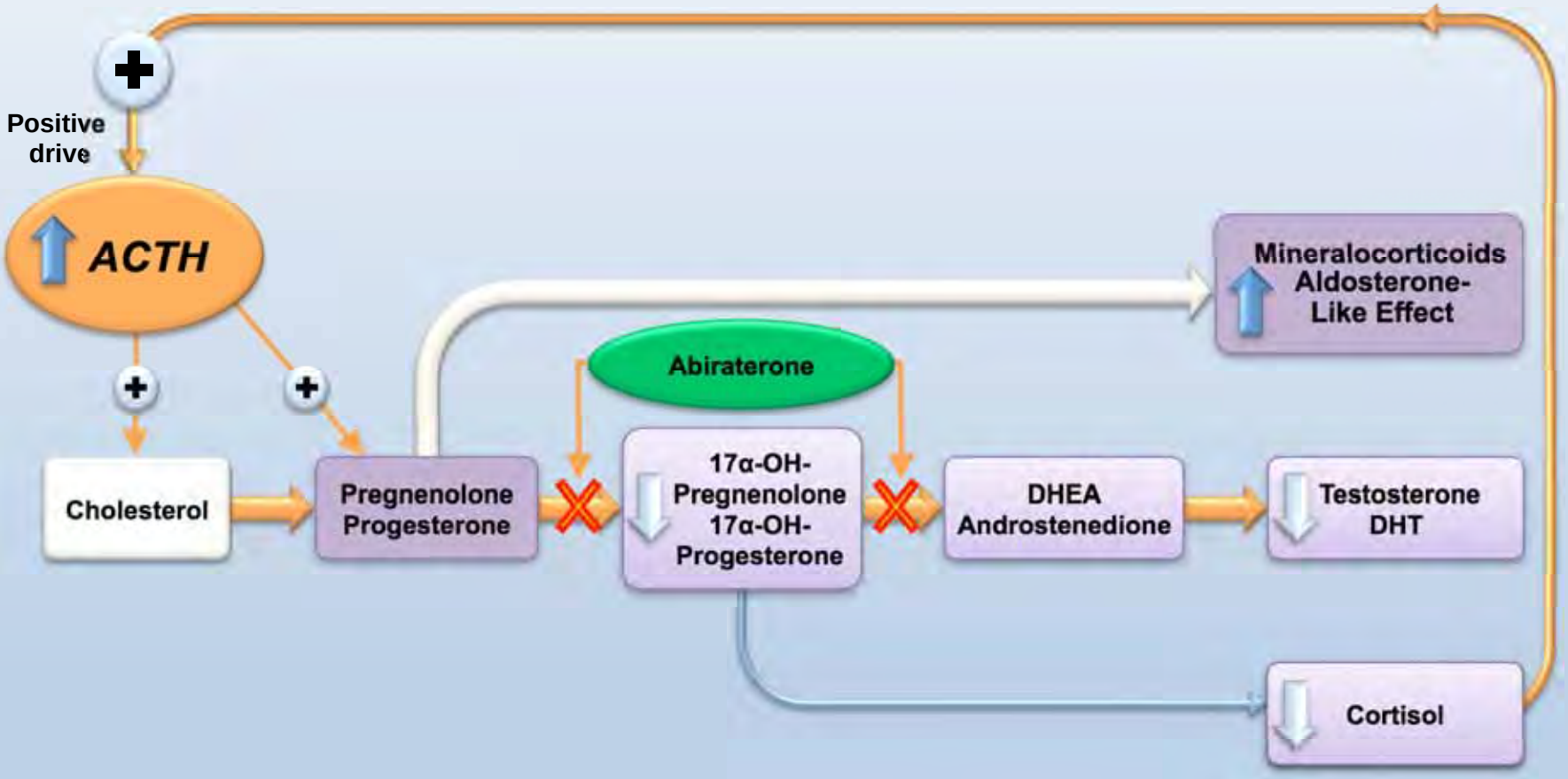
Abiraterone Acetate Adverse Effects



- Most AEs occurred during the first 3 months of treatment
- Most AEs are grade 1-2
- Most common AEs
  - Fatigue
  - Arthralgia
  - Fluid retention-peripheral edema
  - Hypokalemia
  - Hypertension
  - Cardiac Disorders
  - Atrial fibrillation
  - ALT and AST increased
  - Increased hot flashes

De Bono J et al. *N Engl J Med*. 2011;364:1995-2005.

Abiraterone:Why with prednisone?



To block effects of decreased cortisol on increasing ACTH and increased mineralocorticoid effects

Attard G, et al. *J Clin Oncol*. 2008;26:4563.

Incidence of CS-Associated AEs in mCRPC patients

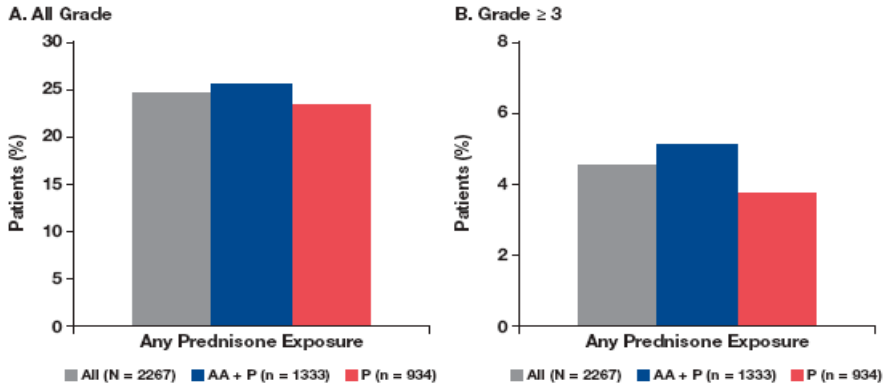


Figure 1. Incidence of CS-Associated All-Grade and Grade ≥ 3 AEs

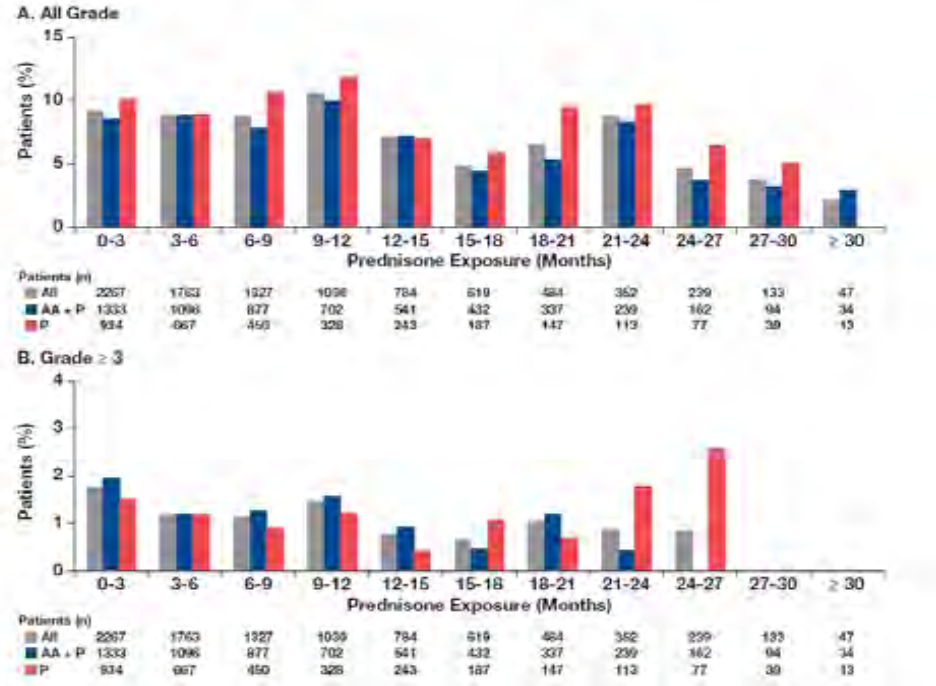


Figure 2. Incidence of CS-Associated All-Grade and Grade ≥ 3 AEs by Exposure

- **Conclusion:** With a median exposure of 8.3 months (range, 0.1-34.9 months; total 2006 years), low-dose P given with or without AA is associated with an overall low incidence of CS-associated AEs, and long-term treatment with AA + P is well tolerated

Assessment of Corticosteroid (CS)-Associated Adve
Events (AEs) With Long-Term Exposure to Low-Dos
Prednisone (P) Given With Abiraterone Acetate (A
to Metastatic Castration-Resistant Prostate Cancer
(mCRPC) Patients

Gomella, et al AUA 2015

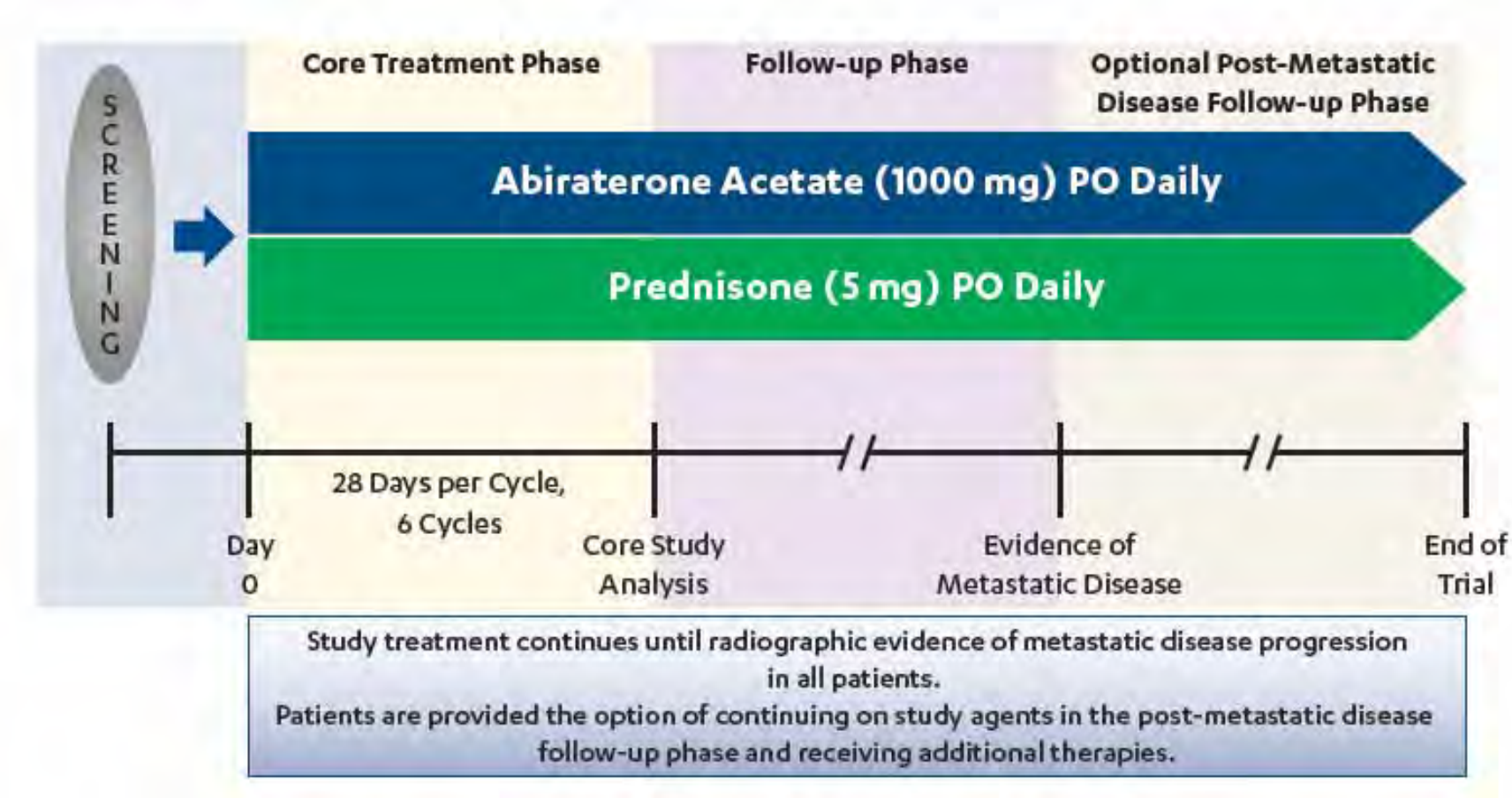
raterone Clinical Trials

ient pulation	Description	Study ID	NCT Number	Phase 2	Phase 3
RPC	Post-chemotherapy	COU-AA-301	NCT00638690		Completed
	Pre-chemotherapy	COU-AA-302	NCT00887198		Completed
n- tastatic PC	M0 with rising PSA despite castrate levels of testosterone	IMAAGEN	NCT01314118	Ongoing, not recruiting	
t breast cer	AA + Exemestane in postmenapausal women with ER+ metastatic breast cancer	BCA2001	NCT01381874	Ongoing, not recruiting	

es not include IIT

2015 www.clinicaltrials.gov

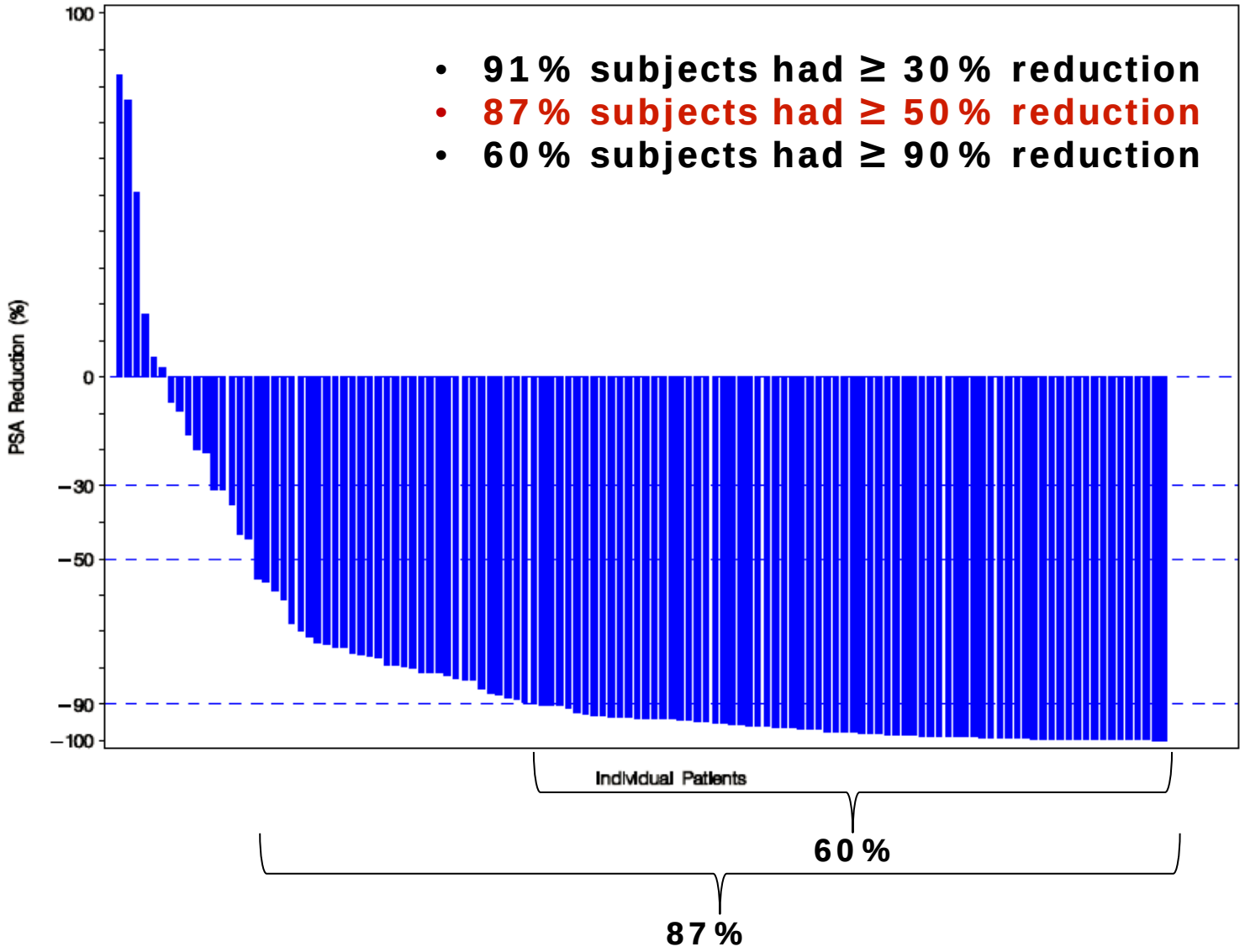
IMAAGEN:
M0 CRPC PSA of ≥ 10 ng/mL/ PSADT of ≤ 10 mo



5 mg pred/day different than label

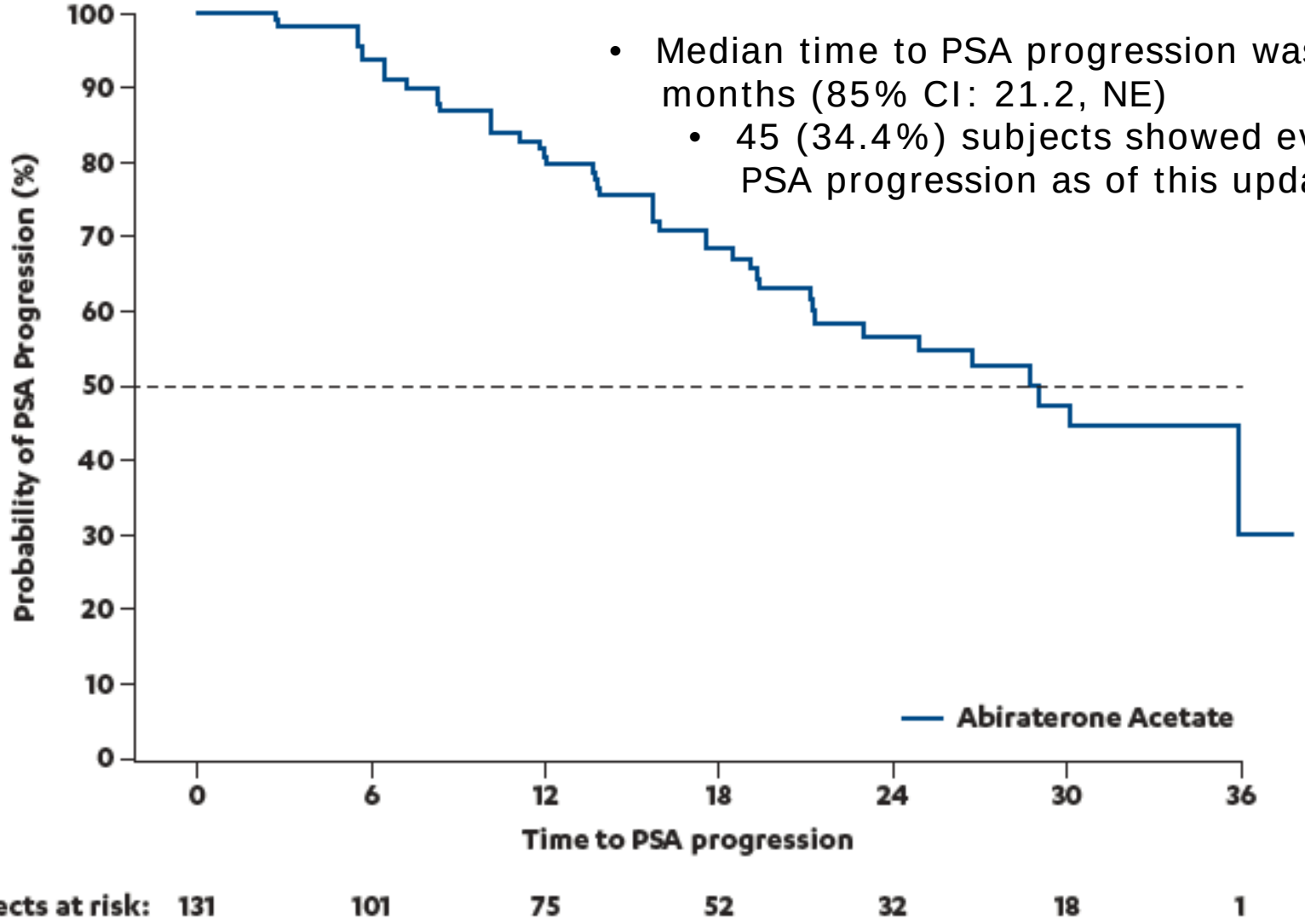
Ryan C, et al. Poster presented ASCO. 2015. Abstract 5053.

PSA Response During Cycles 1-6



Ryan C, et al. Poster presented at ASCO. 2014. Abstract 5086.

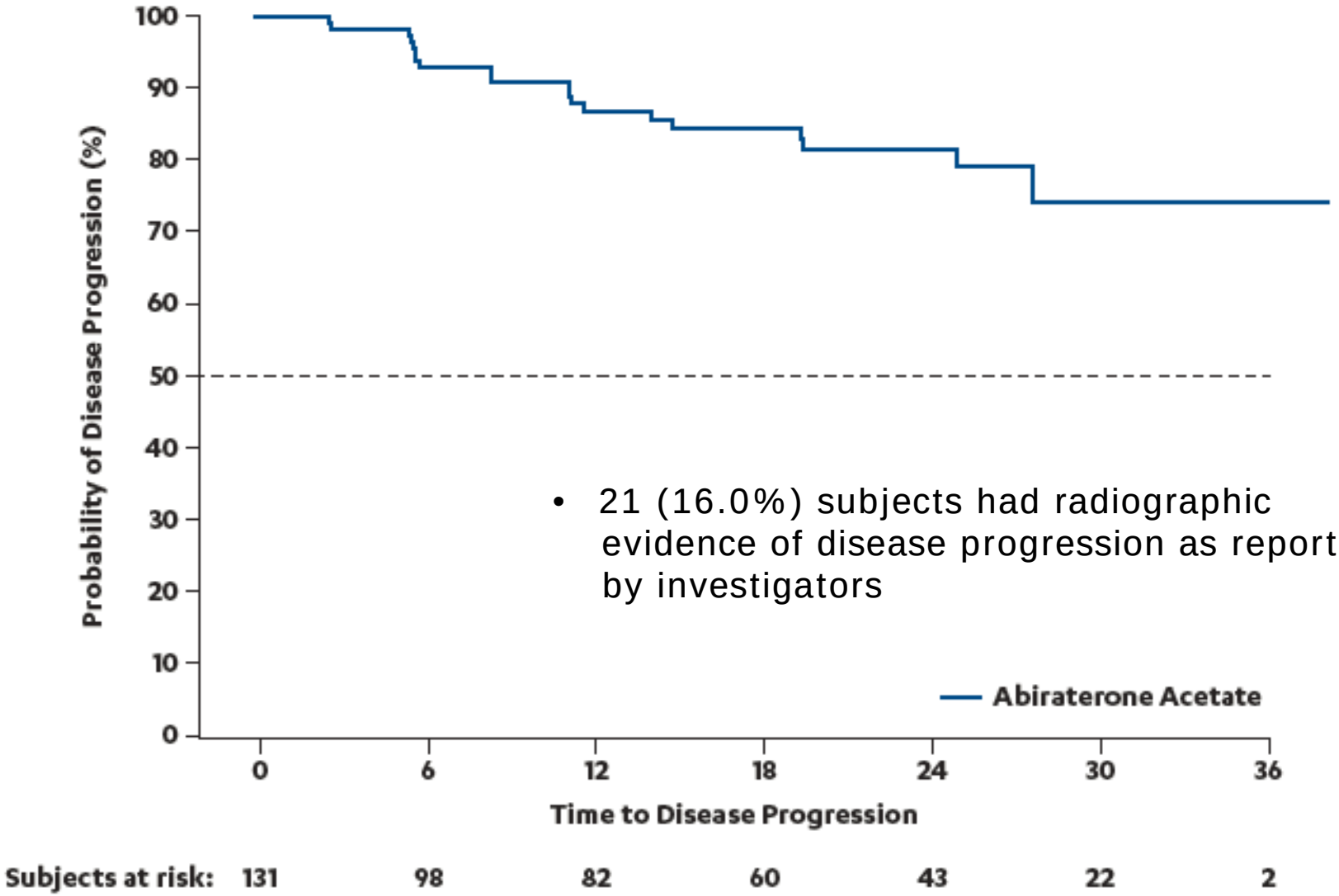
A Progression



- Median time to PSA progression was 28.7 months (85% CI: 21.2, NE)
  - 45 (34.4%) subjects showed evidence of PSA progression as of this update

Ryan C, et al. Poster presented ASCO. 2015. Abstract 5053.

Radiographic Evidence of Disease Progression



- 21 (16.0%) subjects had radiographic evidence of disease progression as reported by investigators

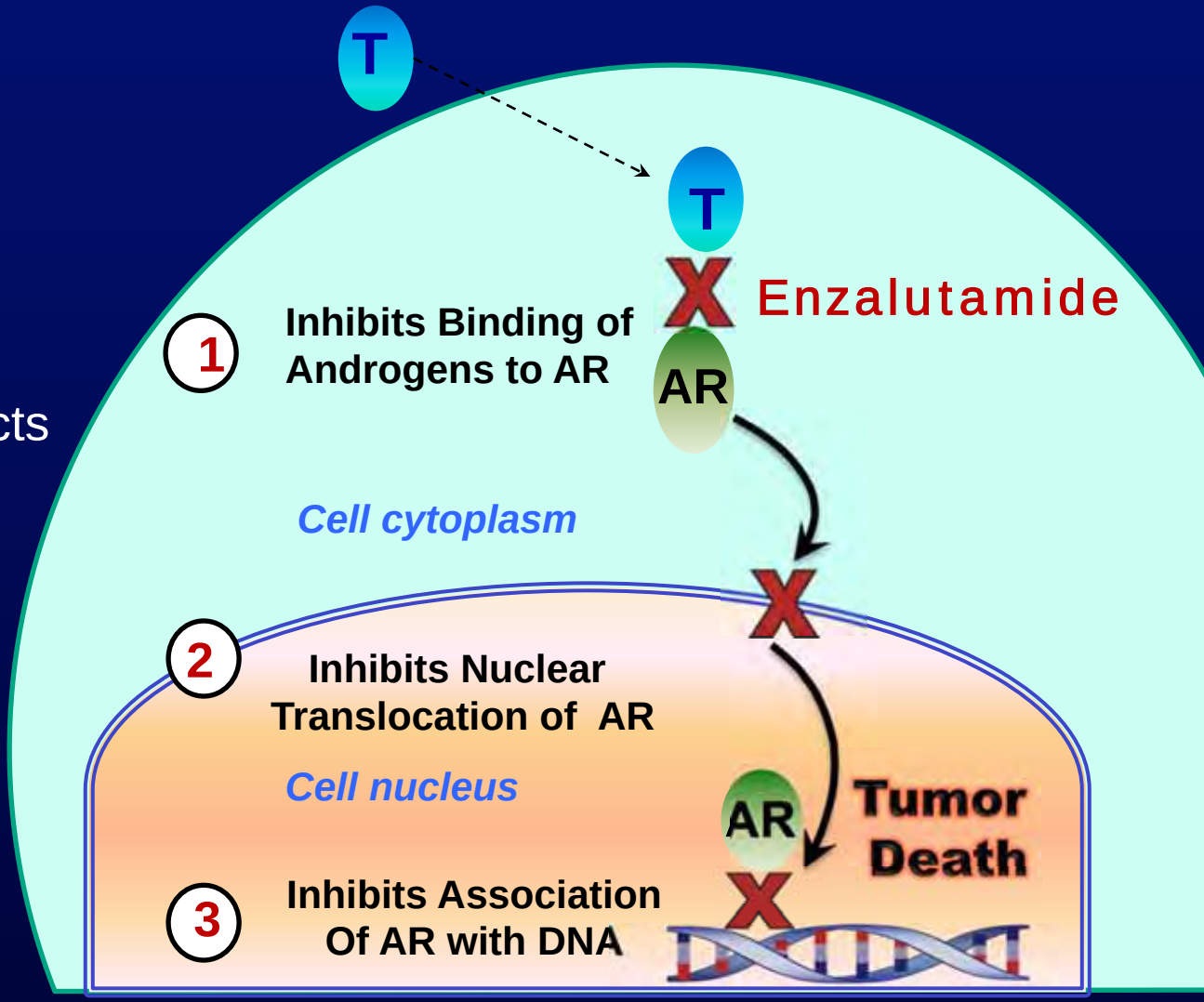
Ryan C, et al. Poster presented ASCO. 2015. Abstract 5053.

MDV3100 (Enzalutamide)
Anti-Androgen with No Agonist Effects

1. MDV3100 oral hormonal agent to target androgen receptor (AR) signaling.

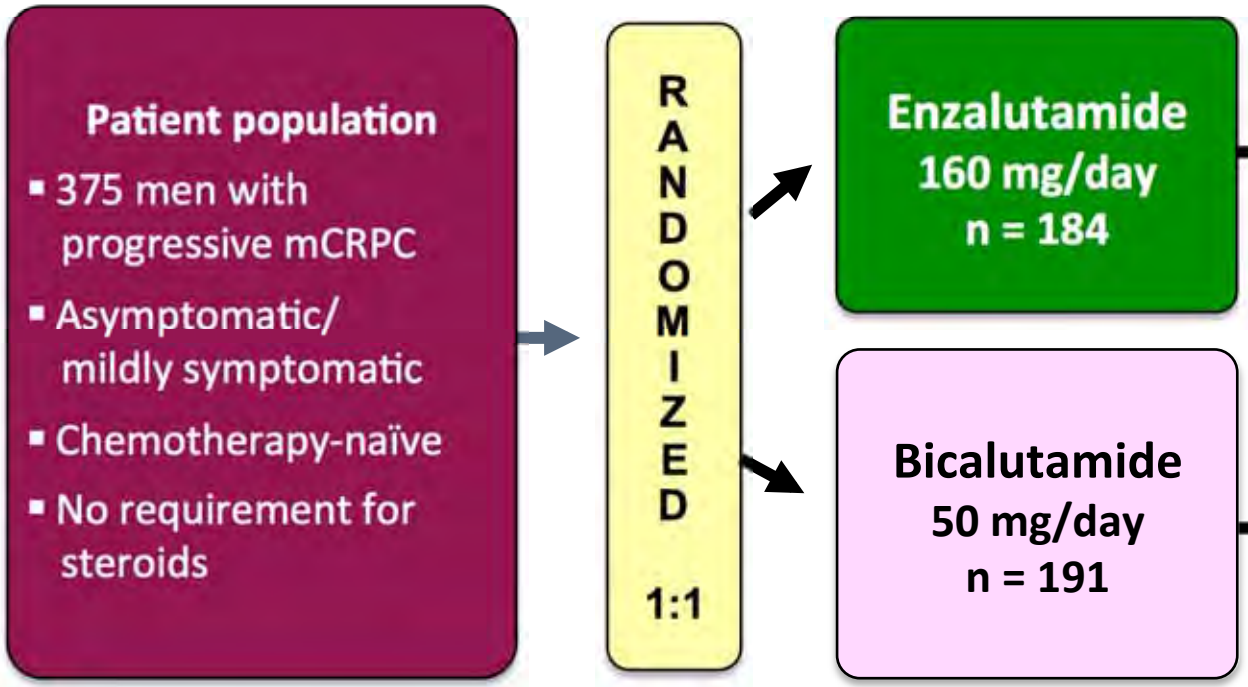
2. A new class of Androgen Receptor Signaling Inhibitors (ARSI) that affects multiple steps in the androgen receptor signaling pathway translocation and DNA binding).

3. No impact on T
4. Does not require steroids



Tran et al. Science 2009;324:787–90.

TERRAIN: A Phase 2 Efficacy and Safety Study of Enzalutamide vs Bicalutamide in mCRPC: Study Design



Primary endpoint

- Progression-free survival, defined as time from randomization to (whichever occurs first):
  - Radiographic progression
  - SRE
  - Initiation of new antineoplastic therapy
  - Death

Secondary endpoints

- PSA response
- Time to PSA progression
- Safety

Statistical design

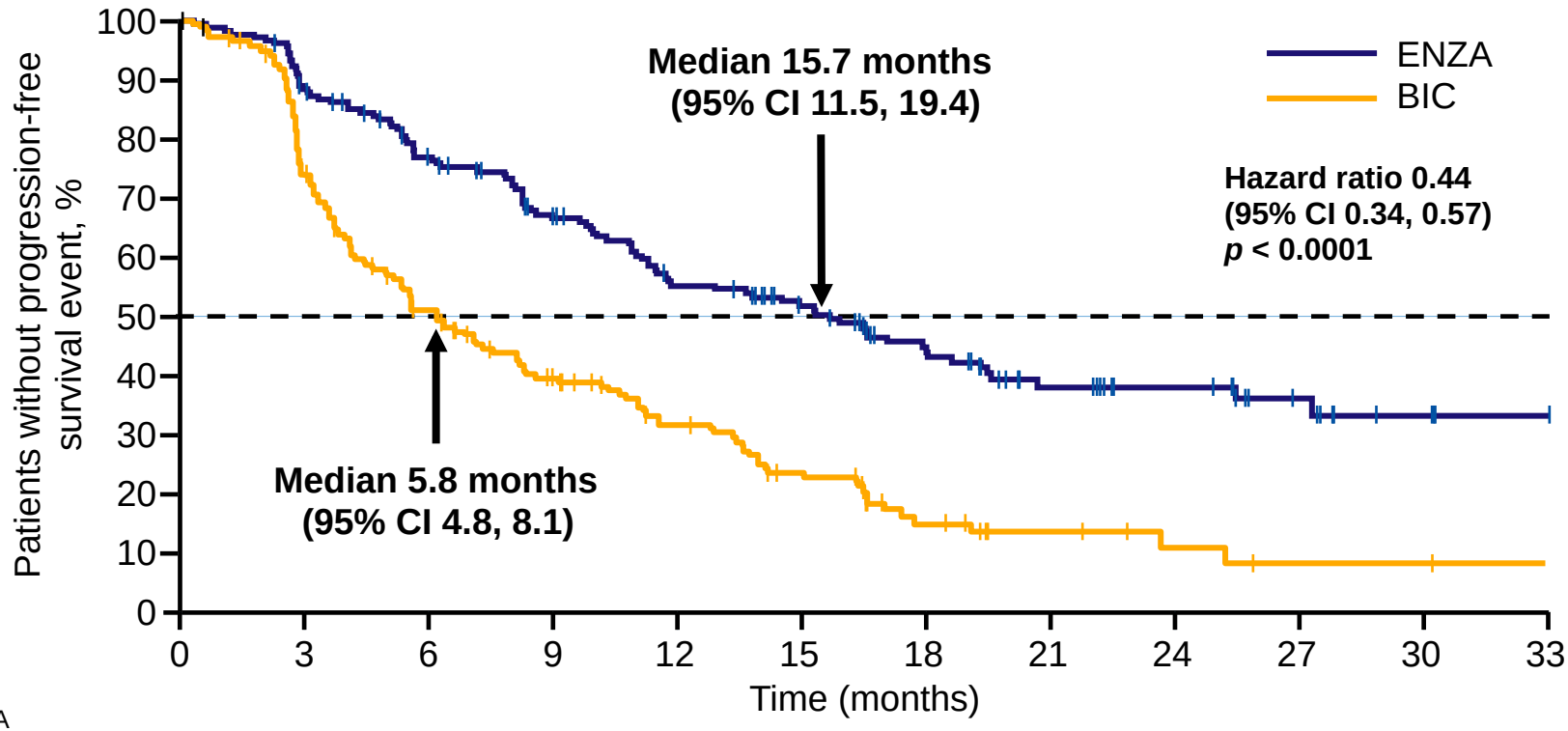
- Final analysis planned at ≥ 220 progression events with 85% power to detect a target hazard ratio of 0.67 (assuming a median PFS of 9 months versus 6 months[1])

mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen; SRE = skeletal-related event

www.clinicaltrials.gov (NCT01288911).

1. Kucuk O, et al. *Urology.* 2001;58:53-58.
Heidenreich A, et al. EAU Congress. March 20-24, 2015; Madrid, Spain.

TERRAIN: A Phase 2 Efficacy and Safety Study of Enzalutamide vs Bicalutamide in mCRPC: Progression-Free Survival

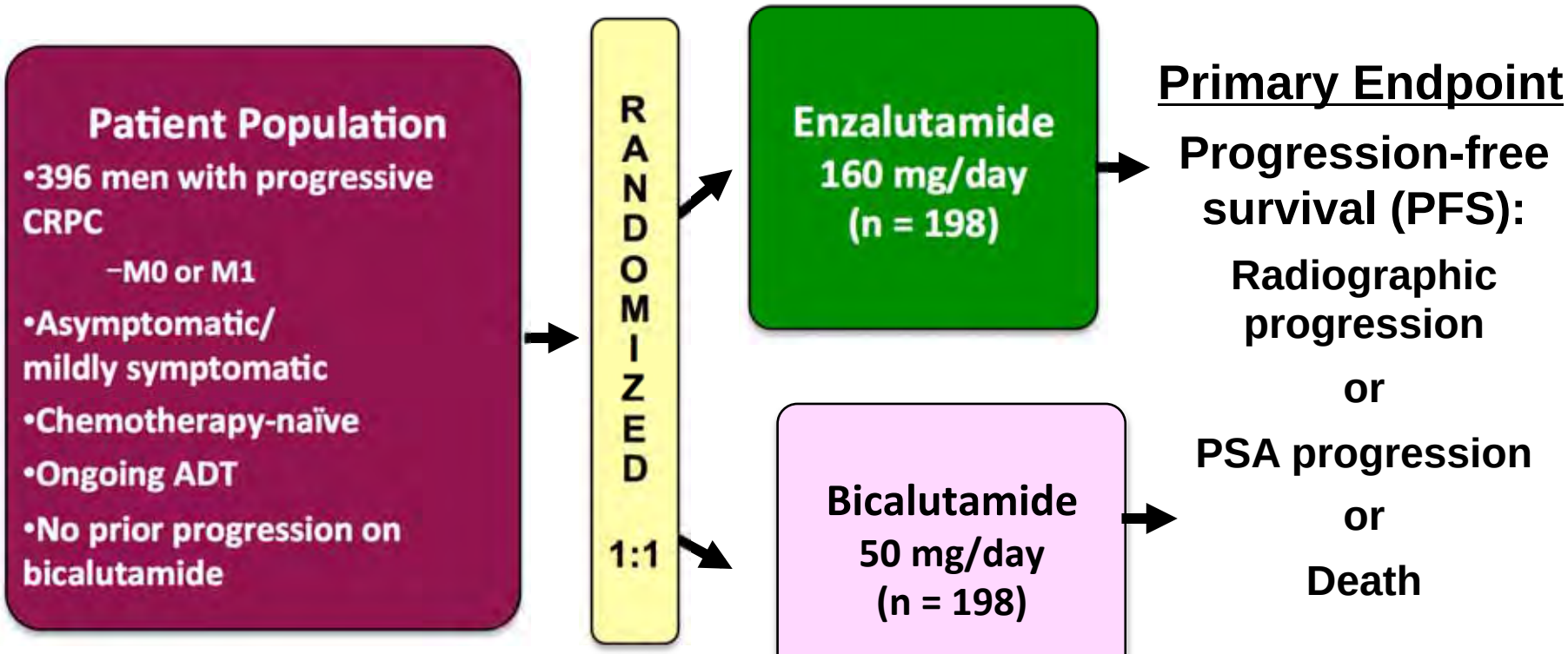


ENZA Patients at risk	184	159	131	107	86	71	52	33	21	13	8	5
BIC Patients at risk	191	133	85	61	44	30	13	7	4	2	2	1

BIC = bicalutamide; CI = confidence interval; ENZA = enzalutamide; mCRPC = metastatic castration-resistant prostate cancer

Heidenreich A, et al. EAU Congress. March 20-24, 2015; Madrid, Spain.

STRIVE: Study Design



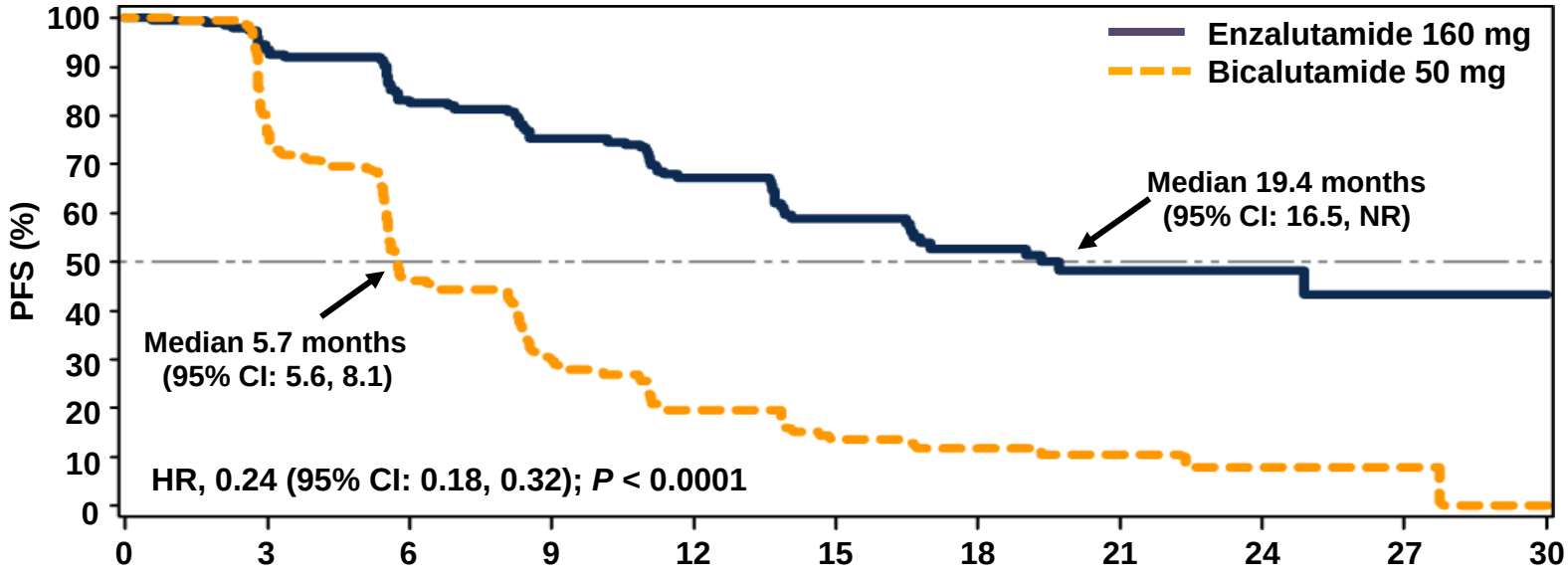
- **Key secondary endpoints:**
  - **Time to PSA progression**
  - **PSA response**
  - **rPFS (M1 population only)**

ClinicalTrials.gov identifier: NCT01664923

ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; M0 = nonmetastatic; M1 = metastatic; PSA = prostate-specific antigen; rPFS = radiographic PFS..

Penson D et al. AUA Annual Meeting. May 15 -19, 2015; New Orleans.

STRIVE: Progression-Free Survival



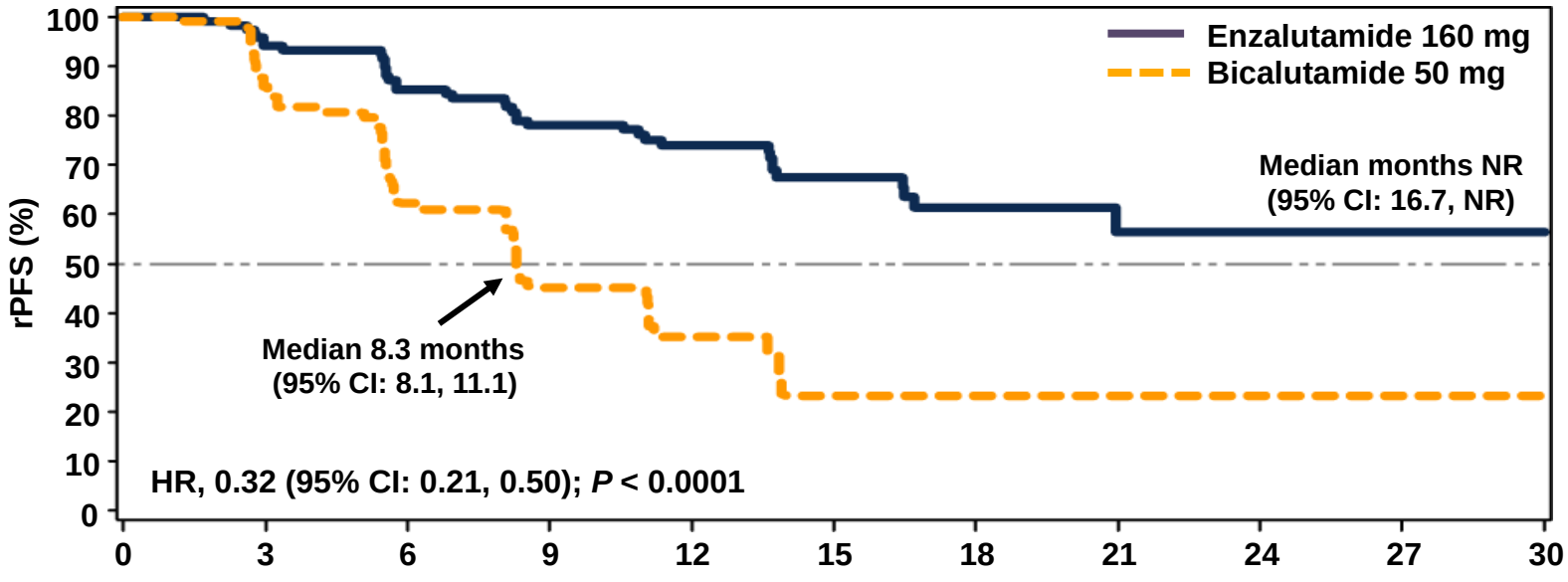
Patients at Risk

Enzalutamide	198	171	150	131	101	66	43	24	16	5	0
Bicalutamide	198	138	80	51	29	17	9	5	3	1	0

CI = confidence interval; HR = hazard ratio; NR = not reached

Penson D et al. AUA Annual Meeting. May 15 -19, 2015; New Orleans

STRIVE: rPFS (radiographic) in M1



Patients at Risk											
Enzalutamide	128	111	94	85	63	40	24	11	7	3	0
Bicalutamide	129	86	46	28	11	5	3	2	1	1	0

- **rPFS defined as the time from randomization to the first objective evidence of radiographic progression (soft tissue or bone) or death from any cause**

CI = confidence interval; HR = hazard ratio; M1 = metastatic; NR = not reached; rPFS = radiographic PFS

Penson D et al. AUA Annual Meeting. May 15 -19, 2015; New Orleans

TRIVE Conclusions

First trial to demonstrate that enza + ADT more efficacious than bicalutamide plus ADT in M0 and M1 CRPC patients:

- Prolonged PFS
- Prolonged time to PSA progression
- Higher PSA response rates
- Prolonged rPFS

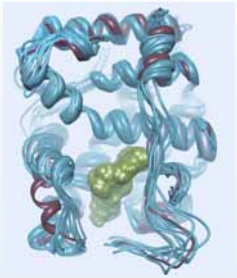
More profound androgen blockade, enza had more fatigue, hot flashes, hypertension more falls and dizziness.

More constipation, diarrhea, anemia, and urinary tract infections were observed in the bicalutamide arm.

Follow up PROSPER phase 3 trial includes only M0 CRPC

Penson D et al. AUA Annual Meeting. May 15 -19, 2015; New Orleans

Enzalutamide Administration

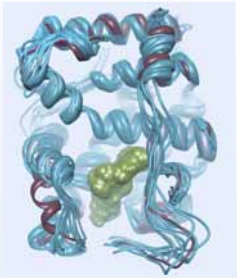


- Administration
  - 160mg (4, 40mg capsules) once daily
  - May be taken with or without food
  - Do not chew, crush, dissolve or open the capsule.

- Dose Modifications
  - If ≥ grade 3 toxicity, delay for 1 week or until symptoms improve to ≤ grade 2, then continue at same or reduced dose

J.M. Gaya, et al. *Expert Review Anticancer Therapy*. 2013:13: 819-827. XTANDI® (enzalutamide) [package insert]. Northbrook, IL:Astellas Pharma US, Inc.; 2013.

Enzalutamide Adverse Events



- Fatigue
- Dizziness
- Hot flash
- Headache
- Peripheral edema
- Infections
- Falls and related injuries
- Lowers seizure threshold
- Diarrhea
- Muscoskeletal Pain
- Hypertension
- LFT abnormalities
- Hallucinations

Escher H et al. *N Engl J Med*. 2012;367:1187-1197.
. XTANDI® (enzalutamide) [package insert]. Northbrook, IL:Astellas Pharma US, Inc.; 2013.

Ongoing Enzalutamide Clinical Trials

nical trial	Phase	Description		Status
TERRAIN CT01288911	2	ENZA vs. bicalutamide after ADT in mCRPC		Data available
STRIVE CT01664923	2	ENZA vs. bicalutamide after ADT in M0/M1 CRPC		Data available
oadjuvant CT01547299	2	Randomized, open-label ENZA neoadj therapy for patients undergoing RP for localized PC		Data available
ATO (TBP) CT01995513	2	Abiraterone + prednisone ± ENZA in patients progressing on ENZA		In follow up
ROSPER CT02003924	3	ADT ± ENZA in M0 CRPC without prior chemotherapy		Open
PWARD T01977651	2	Open-label extension in CRPC patients		Open
RUMPET CT02380274	4	Prospective observational cohort study		Open

Not incuding IIT's

Ongoing Enzalutamide Clinical Trials

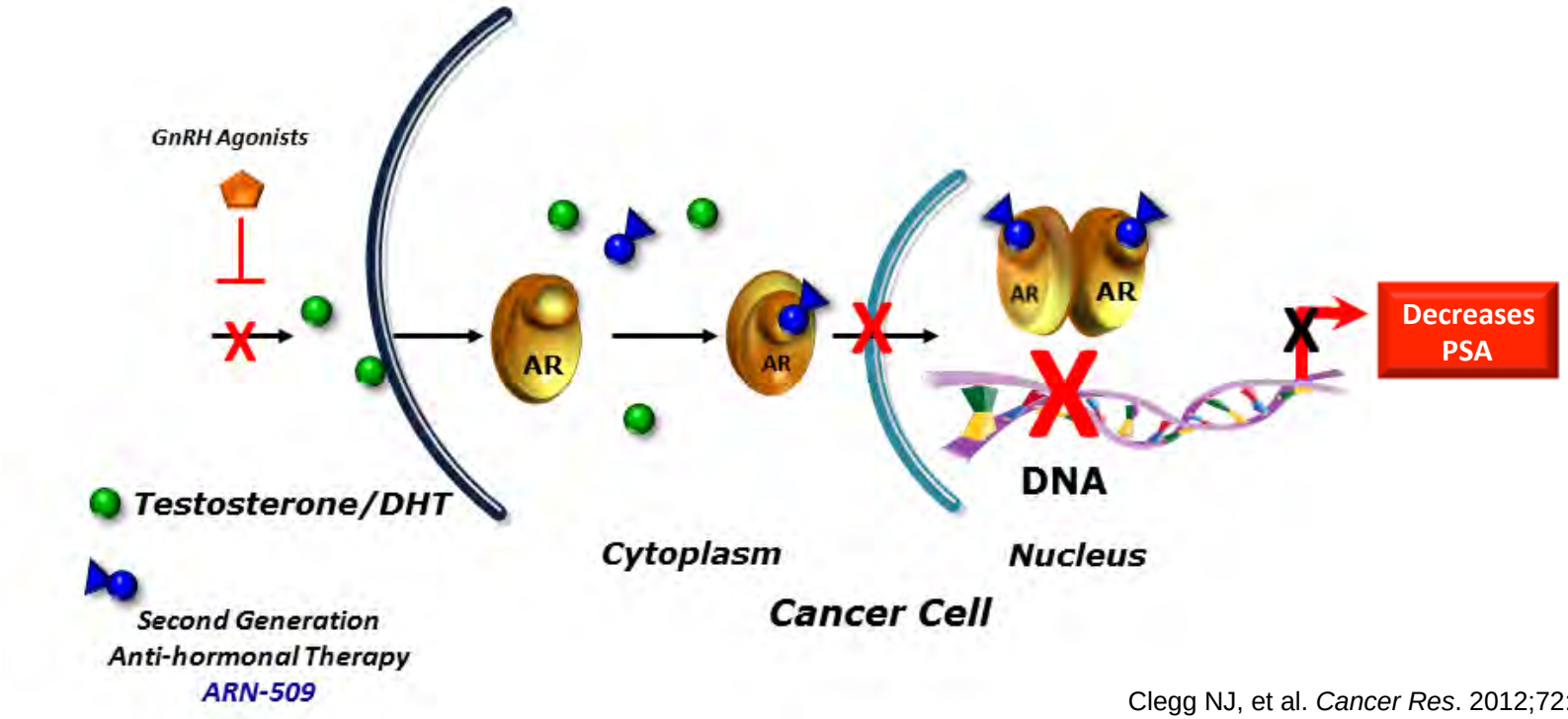
Clinical trial	Phase	Deescription	Status
EMBARK NCT02319837	3	Randomized, 3-arm trial of ENZA vs. ENZA + Leuprolide vs. Placebo + Leuprolide for patients with non-metastatic prostate cancer and rapidly rising PSA after initial local therapy	Open
ASPIRE	4	International Prostate Cancer Registry	Open

Comparison of Abiraterone Acetate and Enzalutamide

	Abiraterone acetate	Enzalutamide
Mechanism of action	CYP17 inhibition	Antiandrogen
Efficacy after docetaxel	OS, PFS	OS, PFS
Efficacy before docetaxel	PFS, OS (NS)	PFS, OS
Major potential adverse effects	Hypertension Hypokalemia LFT abnormalities	Seizures Hypertension ALT elevation
Requires prednisone	Yes	No
Cost	$$$$/-	$$$$

ARN-509 Antagonizes and Blocks Androgen Receptor/DNA Binding and Inhibits Tumor Growth

- ARN-509: competitively inhibits AR-androgen binding; 7-10 X higher affinity than bicalutamide
- AR antagonism impairs AR activation and AR signaling
- ARN-509 inhibits AR-mediated nuclear localization and DNA binding/ transcription



Clegg NJ, et al. *Cancer Res*. 2012;72:1494-1503.

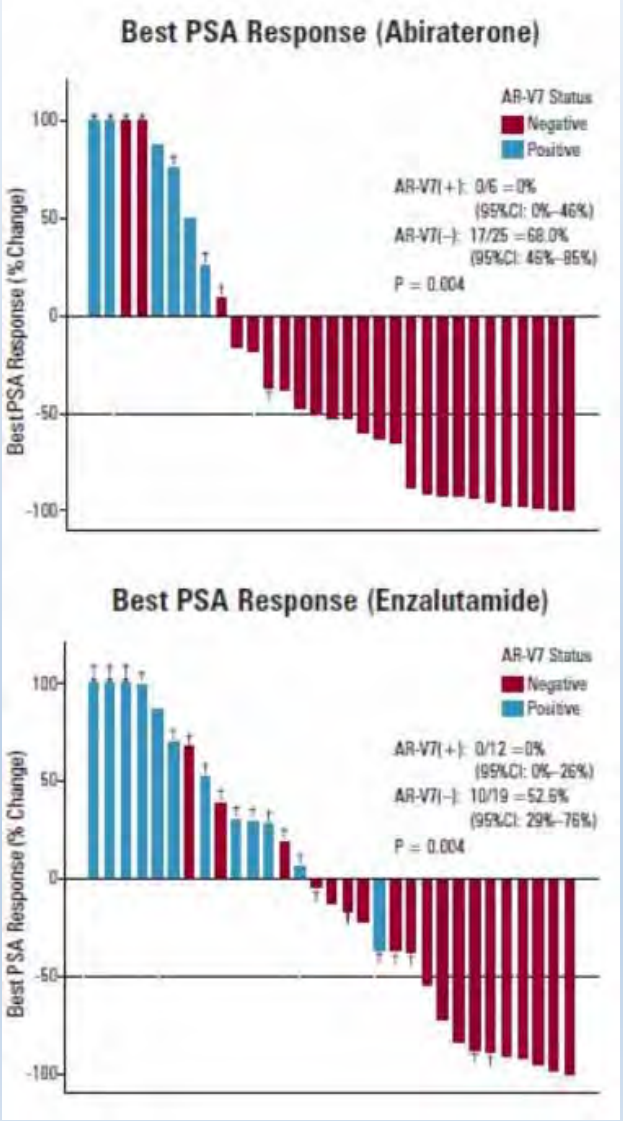
N-509 Clinical Trials

Patient Population	Description	Study ID	NCT Number	Phase 1	Phase 2	Phase 3
Non-metastatic CRPC	M0 patients	SPARTAN	NCT01946204		Currently recruiting	
M1	ARN-509 vs LHRH agonist	-	NCT01790126		Currently recruiting	
mCRPC	Combo w/abiraterone	-	NCT02123758	Currently recruiting		

www.clinicaltrials.gov

Molecular Profiling Precision/Personalized Therapy

- AR-V7: an Androgen Receptor splice variant expressed about 20-fold higher in patients with CRPC
- If present, may indicate resistance to abiraterone or enzalutamide
- May allow more targeted therapies



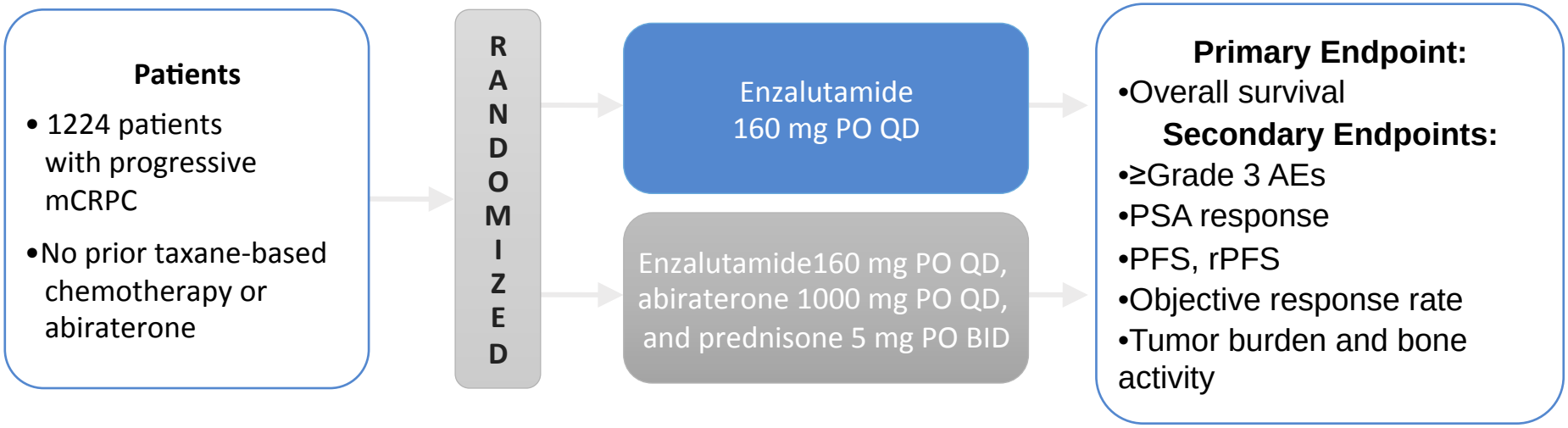
Antonarakis,ES J Clin Oncol 32:5s, 2014 (suppl; abstr 5001)
ES et al. N Engl J Med 2014;371:1028-1038

Abiraterone/Enzalutamide ComboTrials[1]

Phase 2, single-arm combo safety study

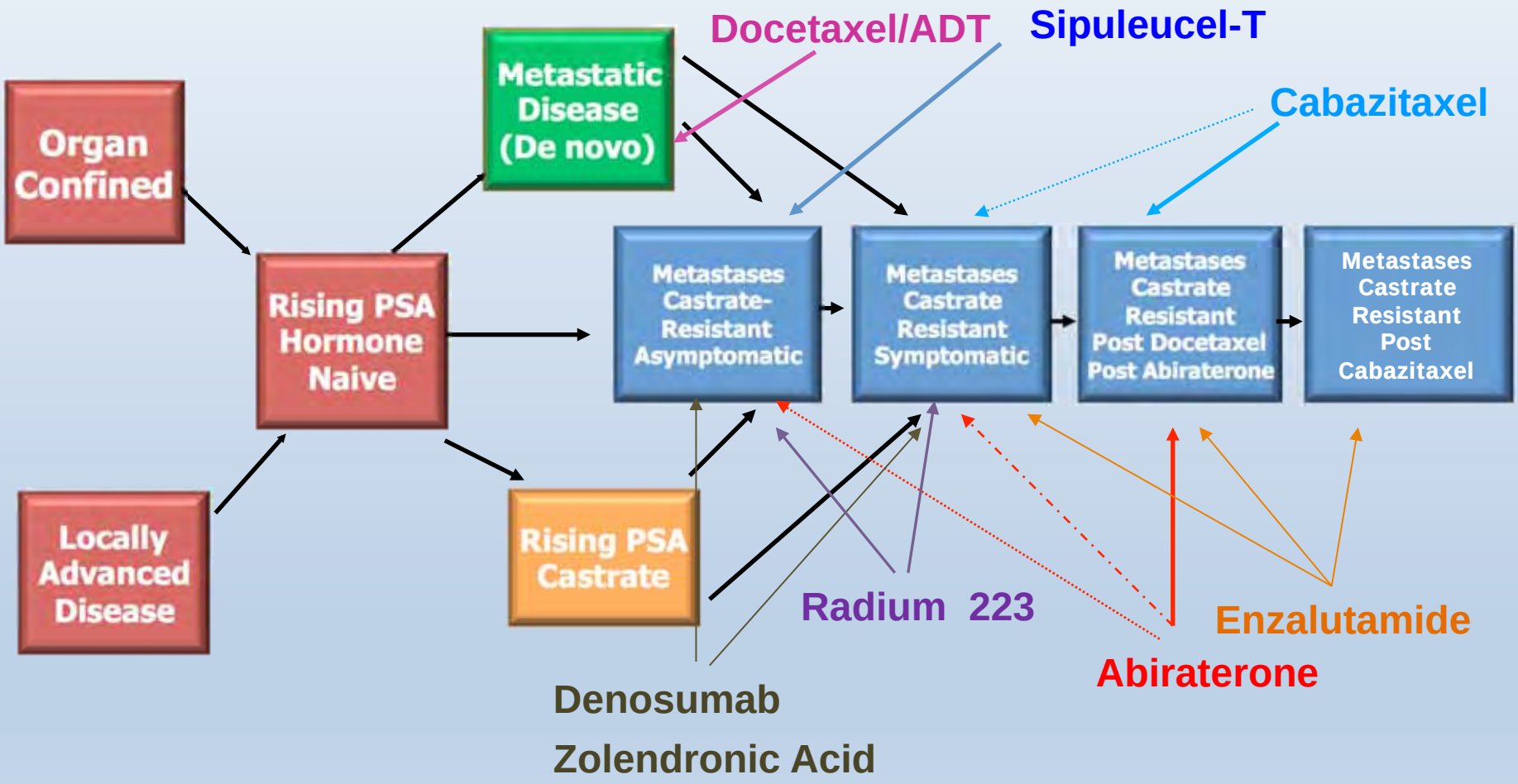
ALLIANCE (formerly ACOSOG, CALGB, NCCTG)

- Phase 3, randomized, open-label
- Estimated completion December 2019



1. http://clinicaltrials.gov.

How to administer, when to administer, and how to combine these newer agents will be an ongoing challenge in the coming years.



Modified from Scher H, et al. Urology 2000

Prostate cancer patients have good reason to hope

New treatments show promise in slowing disease

Karen Weintraub
Special for USA TODAY

Jim Kiefert of Olympia, Wash., has been battling prostate cancer for 23 years. The retired school administrator, 74, has never been more optimistic about his prospects.

For the first time, thanks to a handful of drug approvals over the past 2½ years, there are now multiple options for treating advanced prostate cancer. The newest drug, enzalutamide (brand name Xtandi), came on the market in September with the best survival data ever for prostate cancer.

None of the new drugs is a cure. Re-

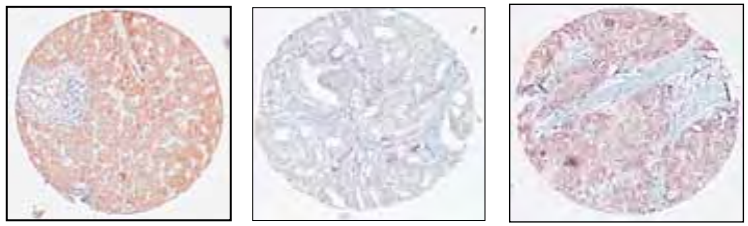
KEVIN P. CASEY FOR USA TODAY

Jim Kiefert, 74, is still rowing and exercising 23 years after his cancer diagnosis. He has benefited from two drug trials in the past decade.

END

Intratumoral Androgen Levels Are Increased Due To Overexpression of The Androgen Synthetic Enzymes

Squaline Monoxygenase



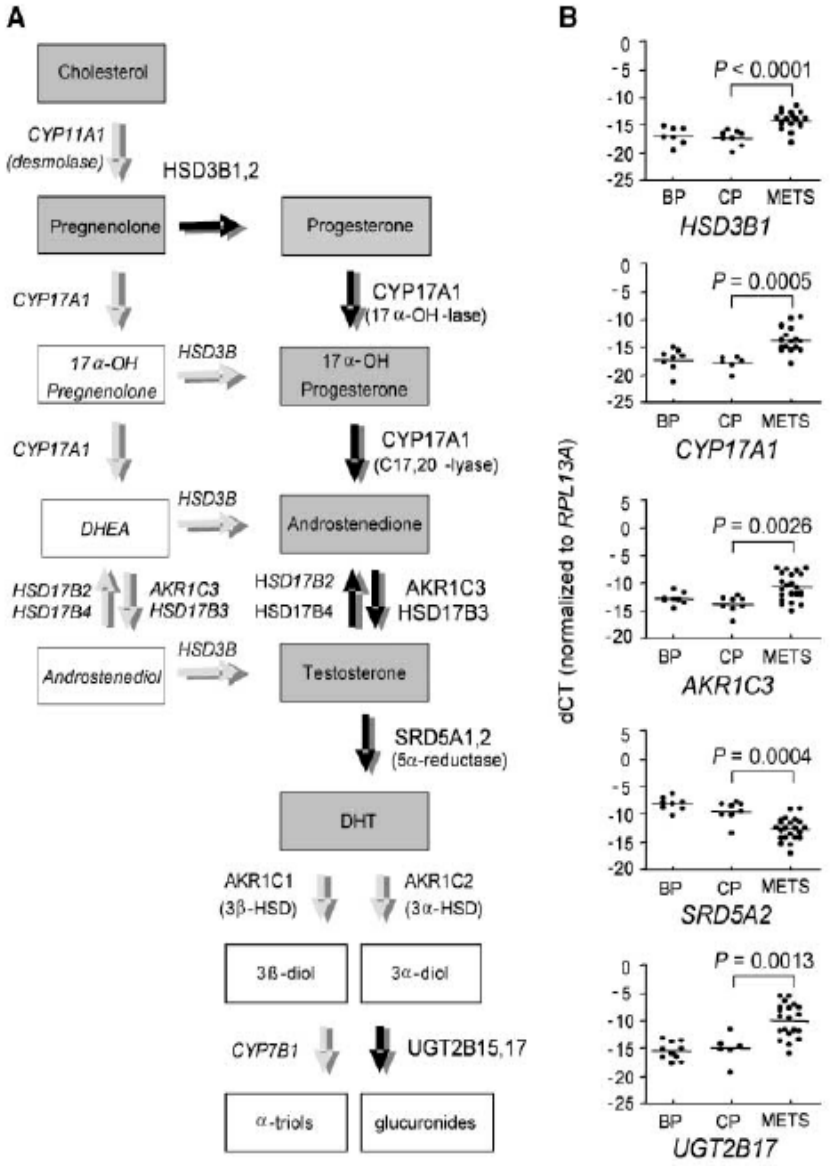
LIVER
Positive control

Non-castrate metastatic

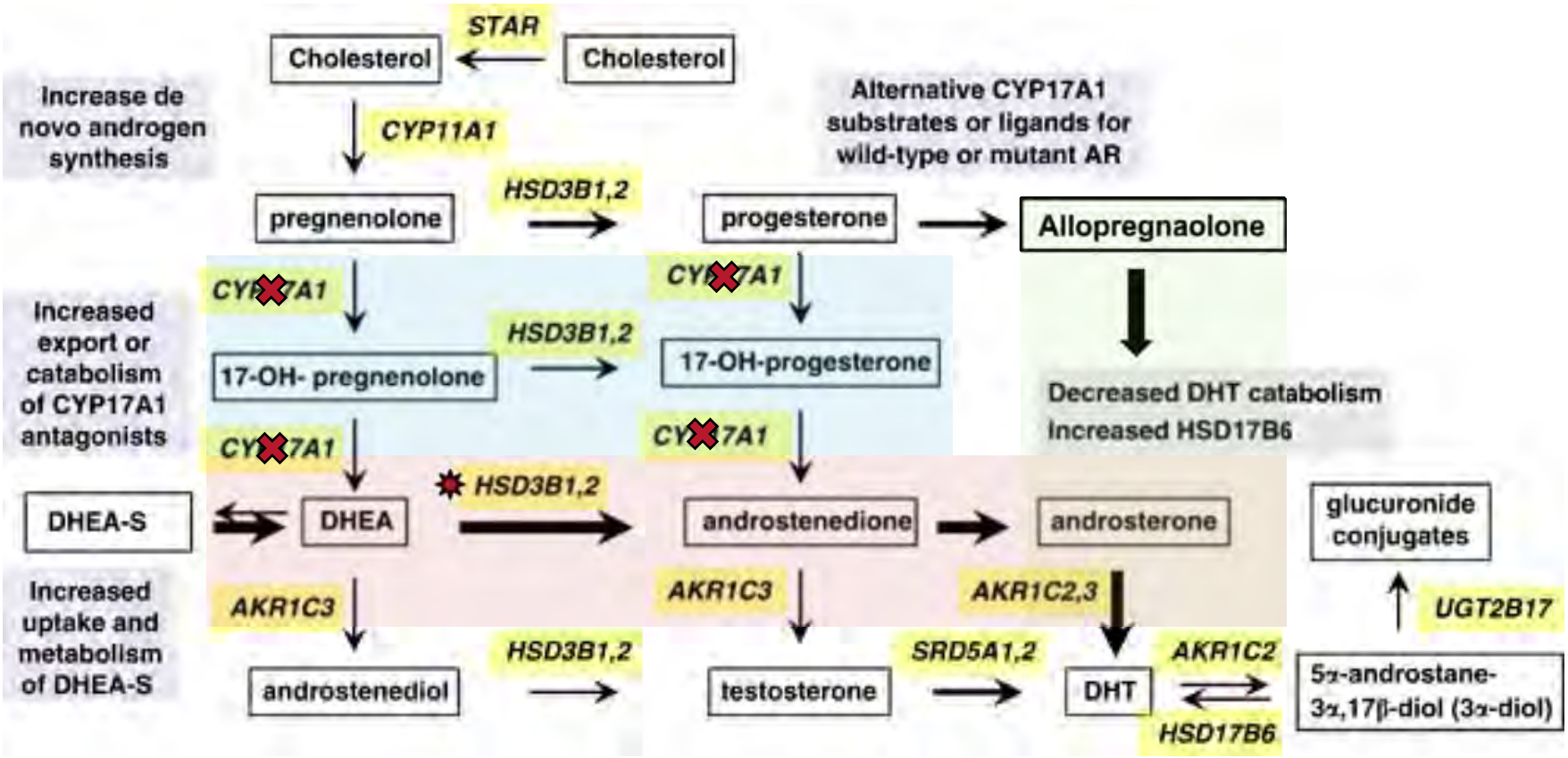
Castrate metastatic

Gerald et al, Amer J Pathol 164:217, 2004

Montgomery et al. Cancer Res 68:4447, 2008



Intracrine Synthesis of Androgens



✸A mutation in 3βHSD1 occurs in a subset of human CRPC tumors that blocks degradation of the enzyme

✖ Abiraterone acetate

Yuan et al., Oncogene, 10 June 2013; doi: 10.1038/onc.2013.235

AR amplifications and overexpression

- Overexpression of AR occurs in the majority of CRPC
  - Elevated gene copy number ~80%
  - High-level of amplification ~30%
  - CTC from mCRPC found high level of gene amplification in 38-63% of the cases
  - AR amplification has correlated to response to second endocrine treatment

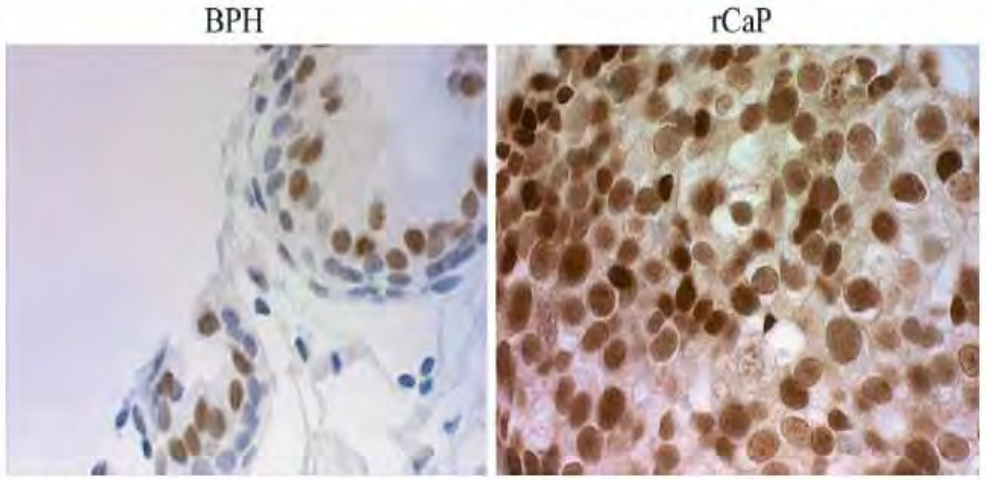


Fig. 1 Photomicrographs of androgen receptor expression. Androgen receptor expression was similar visually in benign prostate (*left*) and recurrent prostate cancer (*right*) obtained by transurethral resection, fixed in formalin, embedded in paraffin, antigen-retrieved, and immunostained with antiandrogen receptor monoclonal antibody. Photomicrographs were reduced from ×400.

Mohler et al., Clin Cancer Res. 10(2):440-8, 2004

- AR gene amplification only partially explains AR overexpression
  - AR regulating miRNAs
  - Deregulation of transcription factors and/or co-regulators
    - NF-κB binds to AR promoter and increases AR mRNA\protein levels
    - Loss RB1 associated with overexpression of AR via increase in E2F1

Waltering et al., Molecular and Cellular Endocrinology 360 (2012) 38-43

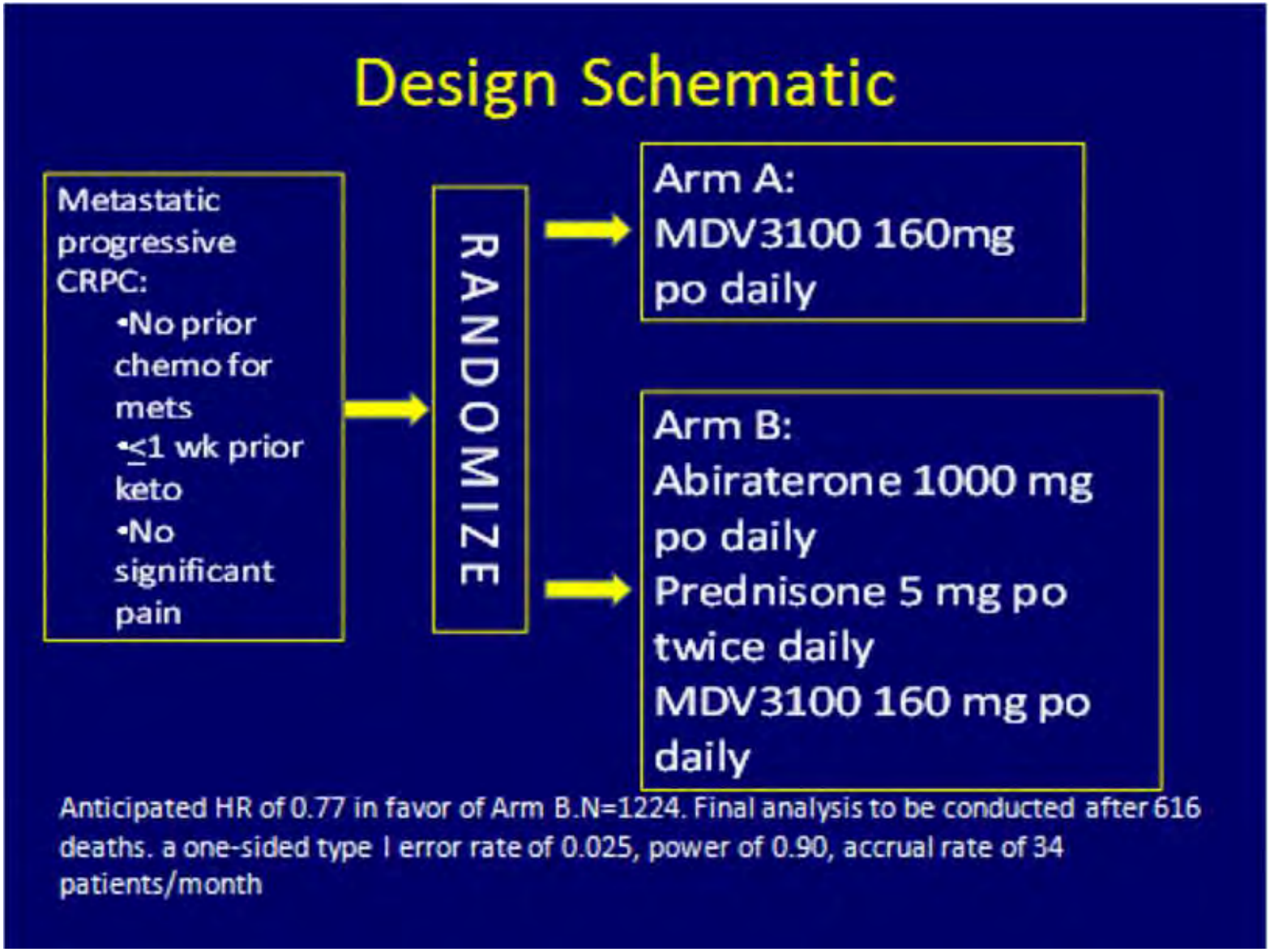
Agents with OS Benefit in mCRPC

Drug	Trial	Comparator	Primary Endpoint	FDA Approval
Chemotherapy-naïve				
Abiraterone acetate + prednisone	COU-AA-302	Placebo + prednisone	OS benefit 5.2 months*	2012
Sipuleucel-T	IMPACT	Placebo	OS benefit 4.1 months	2010
Radium-223	ALSYMPCA	Placebo	OS benefit 3.6 months	2013
Enzalutamide	PREVAIL	Placebo	OS benefit 2.2 months (interim analysis)	2014
Post-chemotherapy				
Abiraterone acetate + prednisone	COU-AA-301	Placebo + prednisone	OS benefit 4.6 months	2011
Enzalutamide	AFFIRM	Placebo	OS benefit 4.8 months	2012
Cabazitaxel + prednisone	TROPIC	Mitoxantrone + prednisone	OS benefit 2.4 months	2010
Docetaxel + prednisone	TAX327	Mitoxantrone + prednisone	OS benefit 2.4 months	2004

*P=0.0151. Did not meet the prespecified value for statistical significance.

Adapted Gomella LG et al. Canadian J Urol. 2014;21:7091

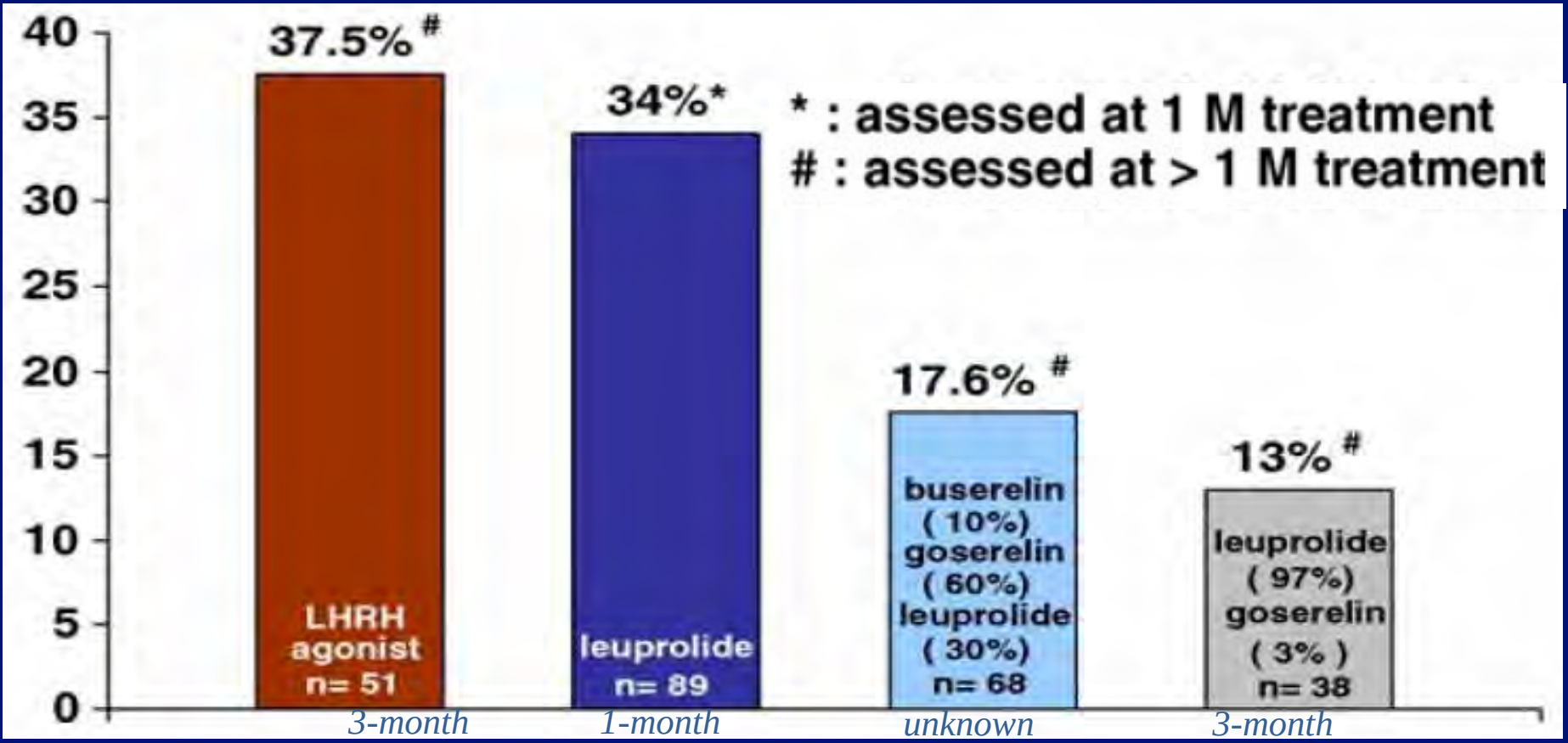
NCI Intergroup Trial – ALLIANCE
PI- Michael Morris



Novel Agents Targeting the Androgen Pathway

Agent	Function	Phase
Abiraterone Acetate	CYP 17 α-hydroxylase\12,20-lyase inhibitor	FDA approved
TAK-700	CYP 17,20 lyase inhibitor	-Phase III
Enzalutamide (MDV3100)	Anti-androgen\androgen receptor signaling inhibitor	FDA Approved
ARN-509	Anti-androgen	-Phase III
AZD3514	AR down-regulator\anti-androgen	-Phase I
TOK-001	Anti-androgen\CYP 17 inhibitor	-Phase I-II
EPI-001	Anti-androgen\N-terminal Domain	-pending clinical trials

Hormone Naïve Disease- Percentage of patients who fai to reach testosterone ≤ 20 ng/dL with LH-RH agonists

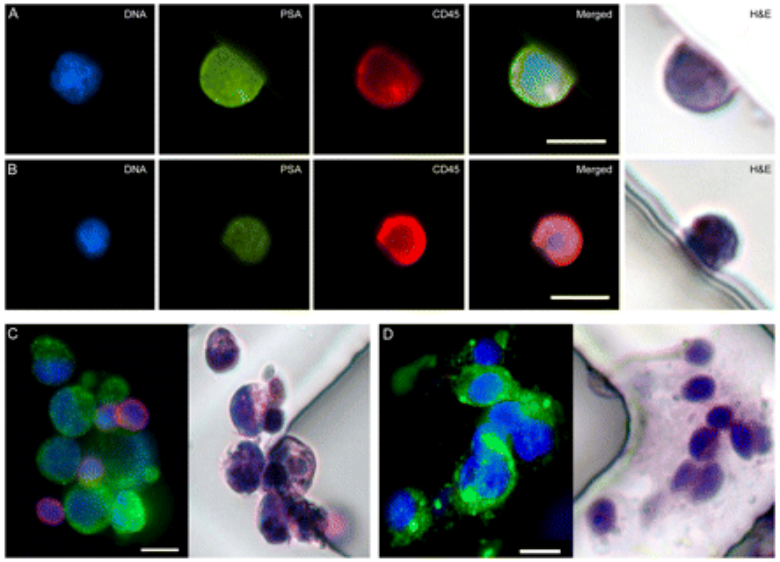


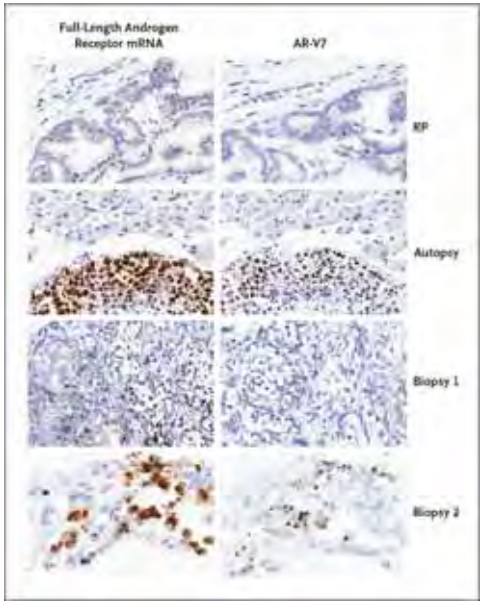
Morote J et al. Urol Int. 2006;77(2):135-8.
McLeod D et al. Urology 2001;58(5):756–61.

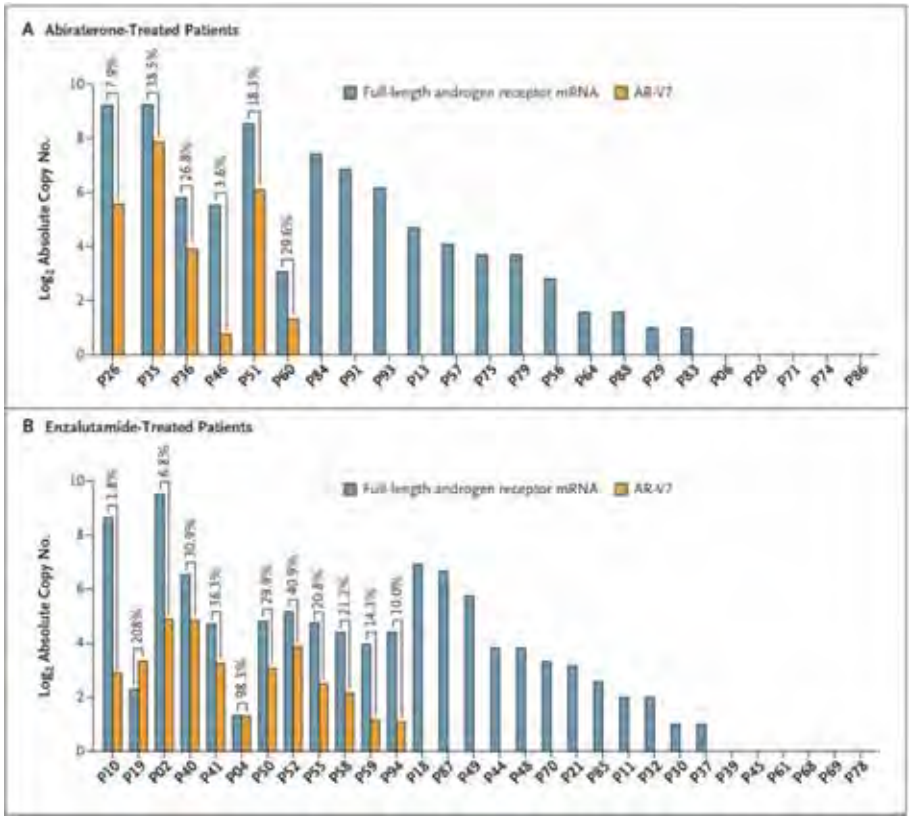
Kawakami J et al. J Urol 2002;167(Suppl. 4):288.
Oefelein MG et al. J Urol 2000;164(3 Pt 1):726–9.

Adapted from Tombal B & Berges R. Eur Urol Suppl 2005;4:30-6

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







Antonarakis ES et al. N Engl J Med 2014;371:1028-1038

Testosterone Levels with GnRH Agents

- Retrospective data: less than half of men taking GnRH analogs have a serum T consistently < 20 ng/dL; Agonists may be beter
- Breakthrough (>50 ng/dL) in about 25% of patients on GnRH analogs
- Currently, castrate level of serum testosterone is defined as ≤50 ng/dL
  - Current definition of castrate level is based on older detection technology (isotop derivative technique)
  - Actual castrate level may be much lower using newer methodologies (eg, radioimmunoassay, chemiluminescence)

Morote J, et al. *J Urol*. 2007;178:1290-1295
Scher HI, et al. J Clin Oncol. 2008;26:1148-1159.
Novara G, et al. Urol Int. 2009;82:249-255.

015 CRPC Treatment Options

- Secondary hormonal manipulation
- Androgen/androgen receptor manipulation
  - Enzalutamide (anti-androgen)
  - Abiraterone Acetate (CYP17 inhibitor, stops adrenal androgens)
- Radiopharmaceuticals
  - Radium 223
- Immunotherapy
  - Sipuleucel-T
- Chemotherapy
  - Docetaxel (1st line)
  - Cabazitaxel (2nd line)

Prostate cancer patients have good reason to hope

New treatments show promise in slowing disease

Karen Weintraub
Special for USA TODAY

Jim Kiefert of Olympia, Wash., has been battling prostate cancer for 23 years. The retired school administrator, 74, has never been more optimistic about his prospects.

For the first time, thanks to a handful of drug approvals over the past 2½ years, there are now multiple options for treating advanced prostate cancer. The newest drug, enzalutamide (brand name Xtandi), came on the market in September with the best survival data ever for prostate cancer.

None of the new drugs is a cure. Re-

KEVIN P. CASEY FOR USA TODAY

Jim Kiefert, 74, is still rowing and exercising 23 years after his cancer diagnosis. He has benefited from two drug trials in the past decade.