Prostate Cancer: Current Management and Future Directions

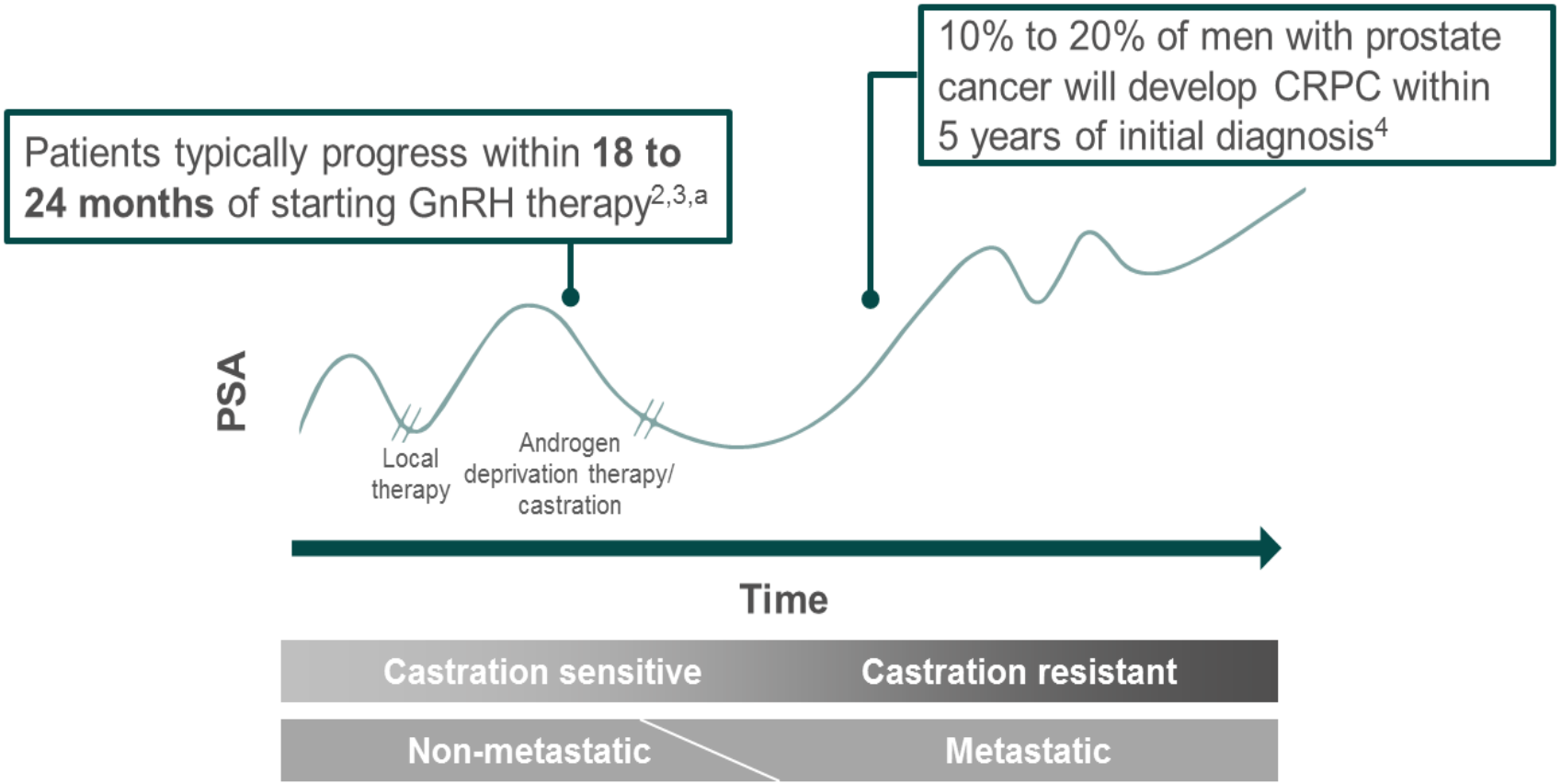
- Alan Koletsky, MD, Medical Oncology
- David Taub, MD, Urology
- Greg Goldin, MD, Radiation Oncology

- Lynn Cancer Institute
- Boca Raton, FL

Prostate Cancer: Current Management and Future Directions – An Overview

1. Review the Natural History of Prostate Cancer
2. Immunotherapeutic Treatment of Prostate Cancer
3. Discuss the Molecular Changes that Accompany the Transition from Hormone-Sensitive to Castration-Resistant Prostate Cancer (CRPC)
4. New Hormonal Therapies for Advanced Prostate Cancer
5. New and Novel Treatment Strategies

Prostate Cancer Progression[1]



Castration-resistant disease: rising PSA value or radiographic progression despite castrate levels of testosterone (≤ 50 ng/dL) and despite androgen deprivation therapy[5]

[a]Or after bilateral orchiectomy.
CRPC, castration-resistant prostate cancer; GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antogen.

1. NCCN Clinical Practice Guidelines: Prostate Cancer v1.2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed October 13, 2015. **2.** Eisenberger MA, et al. *N Engl J Med.*1998;339(15):1036-1042. **3.** Ross RW, et al. *Cancer.* 2008;112(6):1247-1253.

Definition of Castrate Resistant

- NCCN and PCWG2 define CRPC as:
  - Castrate level of testosterone (<50 ng/dL)
  - Disease progression despite ADT demonstrated by rising
  - PSA levels or radiographic evidence
- Term evolved from HRPC/AIPC based on new information on biology of resistance to androgen deprivation therapies
  - Many tumors remain sensitive to novel AR antagonists or androgen synthesis inhibitors
  - Amplifications and mutations in AR develop
  - Synthesis of androgenic precursors increases
  - Not truly hormone refractory

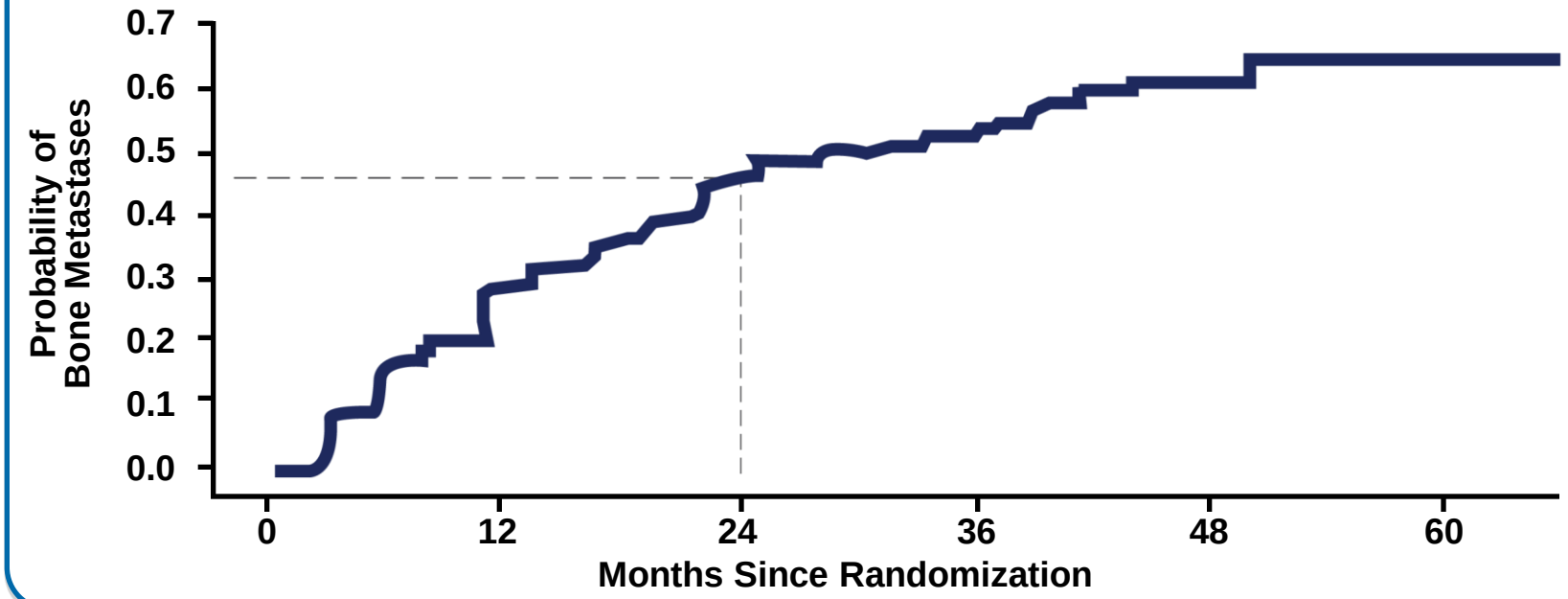
NCCN=National Comprehensive Cancer Network; PCWG2=Prostate Cancer Clinical Trials Working Group 2; HRPC=hormone-refractory prostate cancer; AIPC=androgen-independent prostate cancer; AR=androgen receptor.

Hotte SJ et al. *Current Oncology*. 2010;17:S72-S79; NCCN. Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology. V4.2013; Scher HI et al. *J Clin Oncol*. 2008;26:1148-1159; Mottet N et al. *Eur Urol*. 2011;59:572-583; Bellmunt J et al. *Ther Adv Med Oncol*. 2010;2:189-207; Aggarwal R et al.*Oncologist*. 2011;16:264-275; Antonarakis ES et al. *Clinical Oncol News*. 2011;30-45.

Progression to mCRPC Is Rapid

- 46% of men with CRPC will develop metastases within 2 years

Time to Onset of Metastases in Men With CRPC

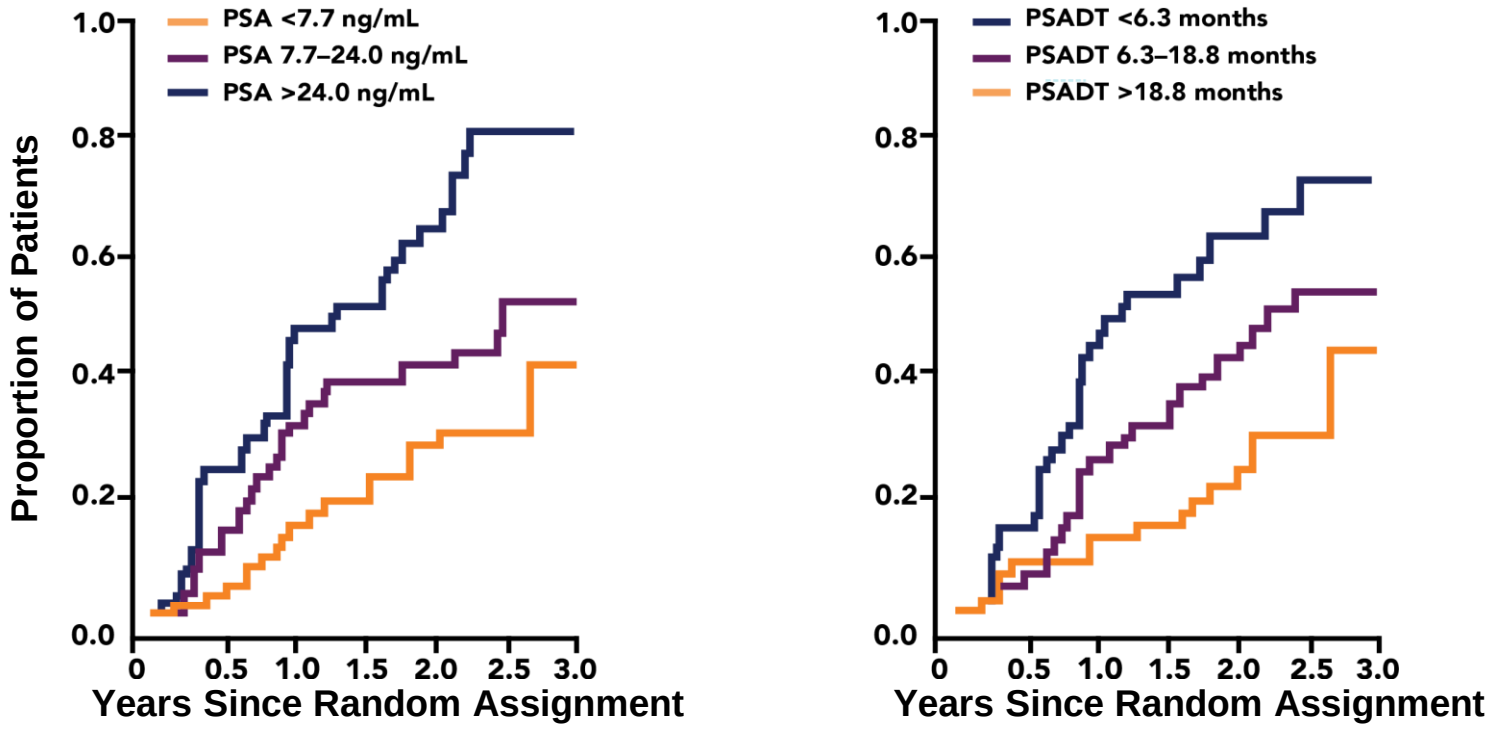


Data are from the placebo arm (n=331) of a randomized, controlled study to evaluate the effects of atrasentan on time to disease progression in men who had progressive CRPC and no radiographic evidence of bone metastases.

Smith MR et al. *Cancer*. 2011;117:2077-2085.

Even Patients With Low PSA or Longer PSADT Are at Significant Risk for Metastatic Disease

Time to Bone Metastases or Death Stratified by PSA and PSADT



Data are from the placebo arm (n=201) of a randomized, double-blind, controlled study to evaluate the effects of zoledronic acid on time to first bone metastases in men with prostate cancer.

PSADT=prostate-specific antigen doubling time.

Smith MR et al. *J Clin Oncol*. 2005;23:2918-2925.

Metastatic Disease Is Often Occult

- Over 30% of men *thought* to have nonmetastatic CRPC were found to have metastatic disease when screened via imaging for a recent clinical trial

Leading Cause of Screening Failures	Patients (N=2577)
Detection of metastatic disease	818 (32%)

Data represent screening failures of patients trying to enroll in the phase 3 study comparing zibotentan with placebo. Of the 2577 patients, 818 who were presumed to have nonmetastatic CRPC actually had metastatic disease and did not qualify for the study.

Yu EY et al. *J Urol.* 2012;188:103-109.

Radiographic Methods* for the Identification of Prostate Cancer Metastases

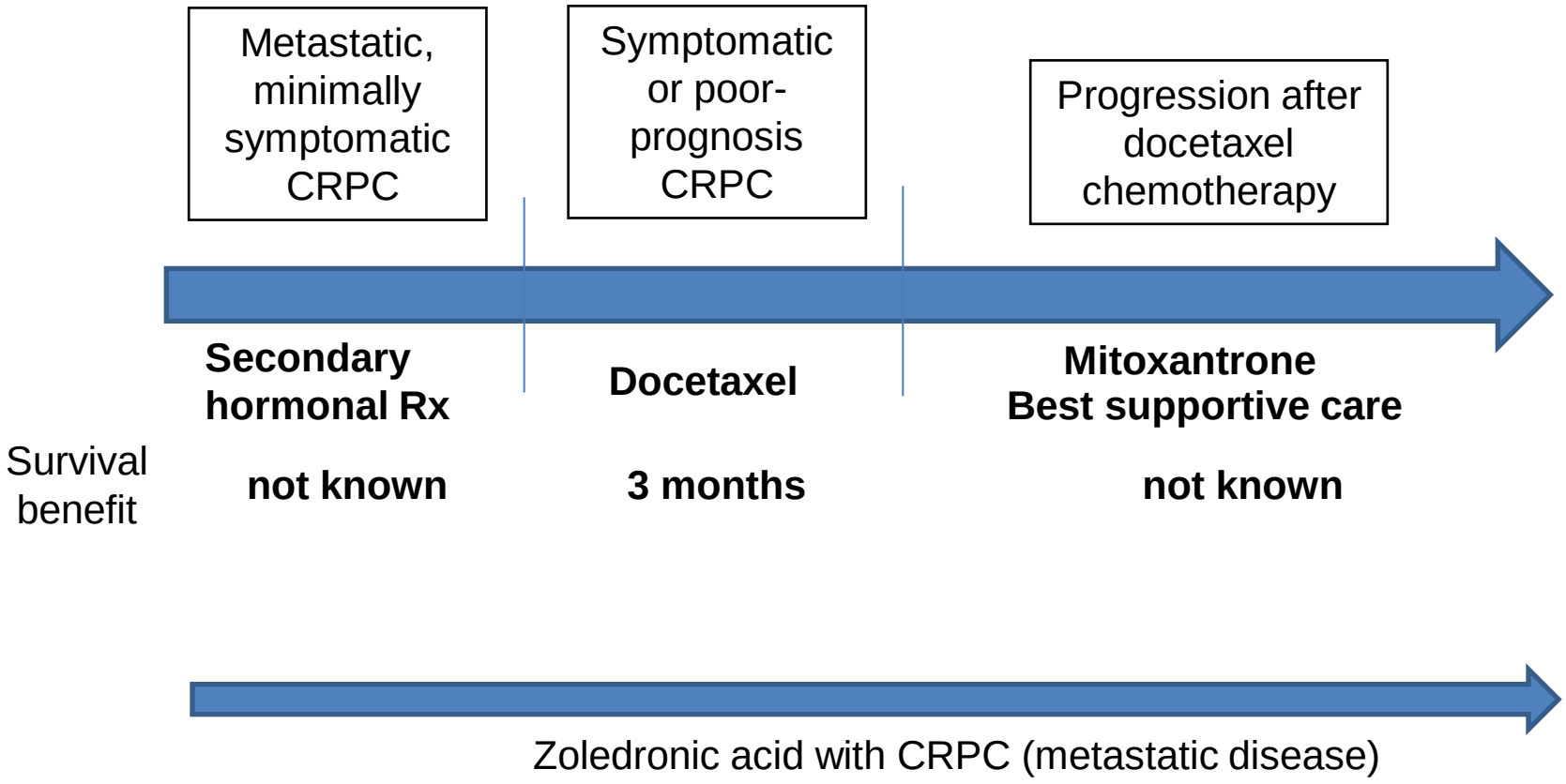
Radiographic Methods

Method	Description	Sensitivity/Specificity
MRI	Provides an image of zonal anatomy. Useful in the detection of extracapsular extension or seminal vesicle invasion	Sensitivity 73% to 80% and high specificity for localized disease
CT	May be useful in staging; however, smaller nodes occurring earlier in disease may not be detected	Broad variation in sensitivity and specificity reported
Bone scan (MDP-mTc^{99} scintigraphy)	Identifies bone metastases based on active osteoblastic activity and turnover	Sensitivity may range from 39% to 94%, specificity is as high as 89%. However, negative results do not necessarily always rule out bone metastases and newer modalities must be validated
^{18}F-Sodium Fluoride PET/CT (NaF PET/CT)	NaF has a high affinity for osteoblastic activity	High sensitivity (100%) and specificity (100%) reported in one study; however, rigorously controlled prospective trials may be needed

*There are no definitive guidelines for methods of identifying CRPC.

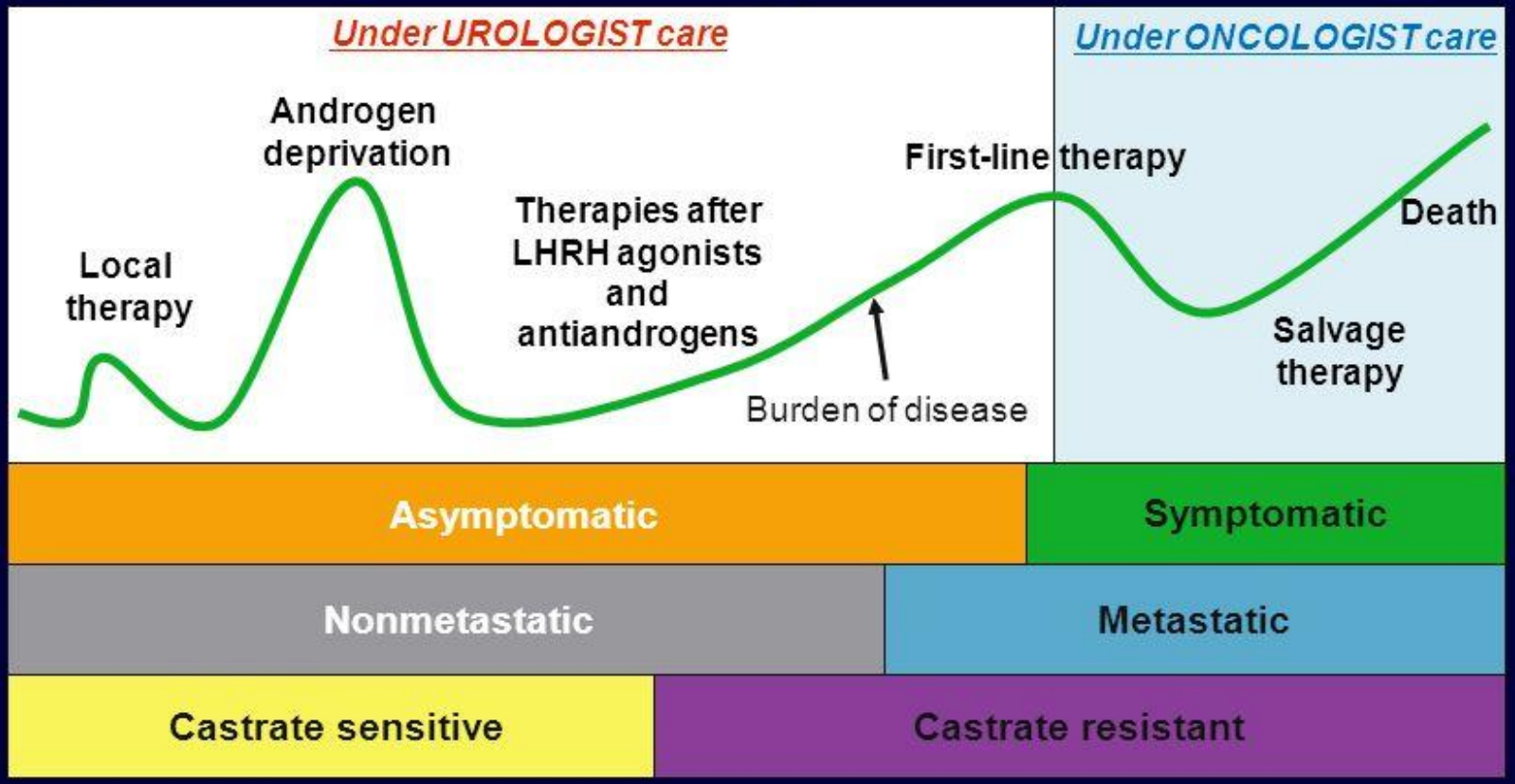
Abdellaoui A et al. *Future Oncol*. 2011;7:679-691; Hricak H et al. *Radiology*. 2007;243:28-53; Even-Sapir E et al. *J Nucl Med*. 2006;47:287-297; Fox JJ et al. *Acta Oncol*. 2011;50(suppl 1):39-48; Brown MS et al. *Nucl Med Commun*. 2012;33:384-394.

Sequencing CRPC Therapy – 2010



Natural History of Prostate Cancer

- Typical patient presentation as they move through different stages



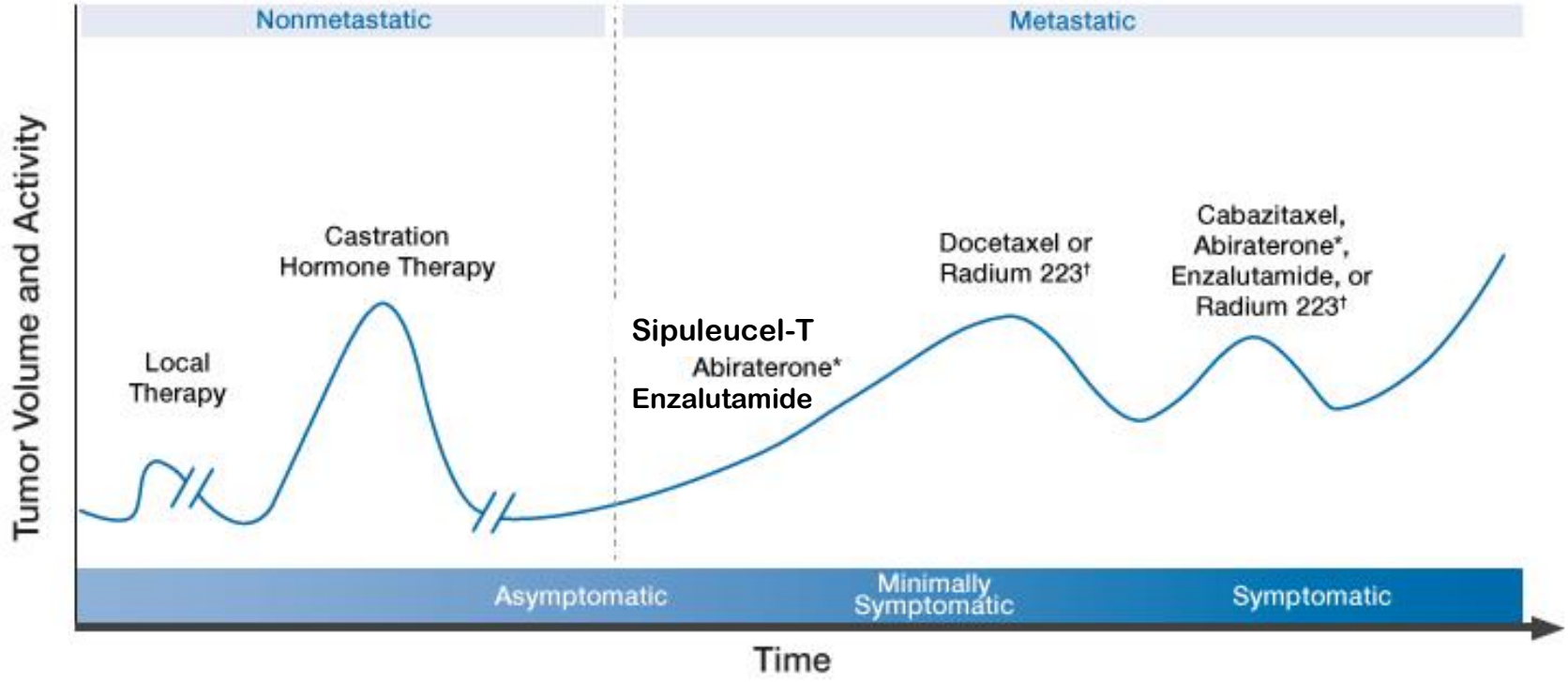
Higano C, et al. In: Figg WD, et al. Drug management of prostate cancer; 2010.

Since 2010, 7 New Therapies Have Shown Clinical Benefit for Patients withmCRPC

- Sipuleucel-T: immunotherapy for men with asymptomatic to minimally symptomatic mCRPC (IMPACT)
- Cabazitaxel: second-line chemotherapy for mCRPC (TROPIC)
- Abiraterone acetate: in combination with prednisone in the pre- and postchemotherapy setting (COUGAR 302, COUGAR 301)
- Denosumab: for SRE prevention in mCRPC
- Enzalutamide: treatment of mCRPC in the pre- and postdocetaxel setting (AFFIRM, PREVAIL)
- Radium 223: treatment of CRPC with symptomatic bone metastases and no known visceral disease in the pre- and postdocetaxel setting (ALSYMPCA)
- Docetaxel: chemotherapy for treatment of mCRPC (TAX 327)

Kantoff PW et al. *N Engl J Med*. 2010;363:411-422; De Bono JS et al. *Lancet*. 2010;376:1147-1154; De Bono JS et al. *N Engl J Med*. 2011;364:1995-2005; Fizazi K et al. *Lancet*. 2011;377:813-822; Scher HI et al. *N Engl J Med*. 2012;Epub; Xofigo [package insert]. Wayne, NJ:Bayer Healthcare; 2013.

The Therapeutic Landscape of Prostate Cancer Today



*Abiraterone is FDA-approved across mCRPC.

†Radium 223 is indicated for patients with symptomatic bone metastases and no visceral metastases.

Higano CS. Springer Science+Business Media, LLC. 2010:321-327; NCCN. Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology. V4.2013.

Chemotherapy – Historical Use in Metastatic Castration-Resistant Patients

Usually Reserved for CRPC Patients who were

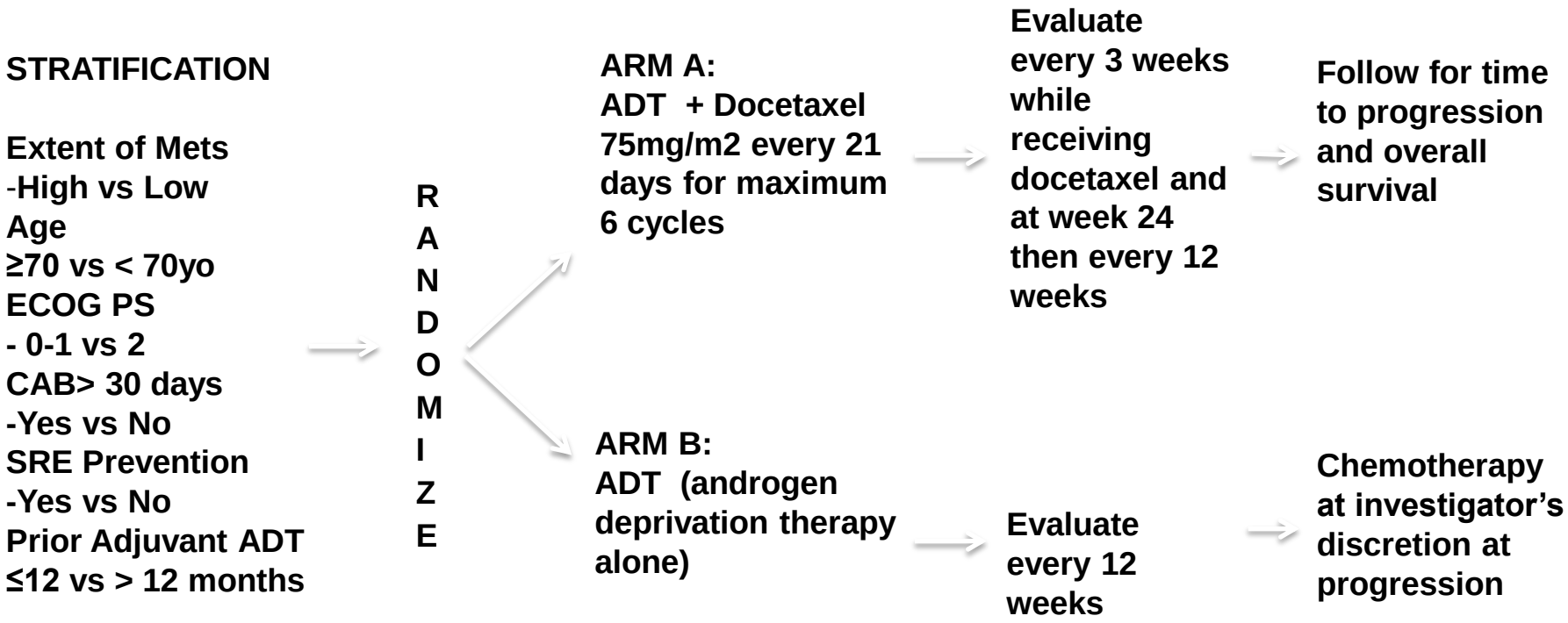
Symptomatic

Rapidly Progressing

Had Visceral Disease

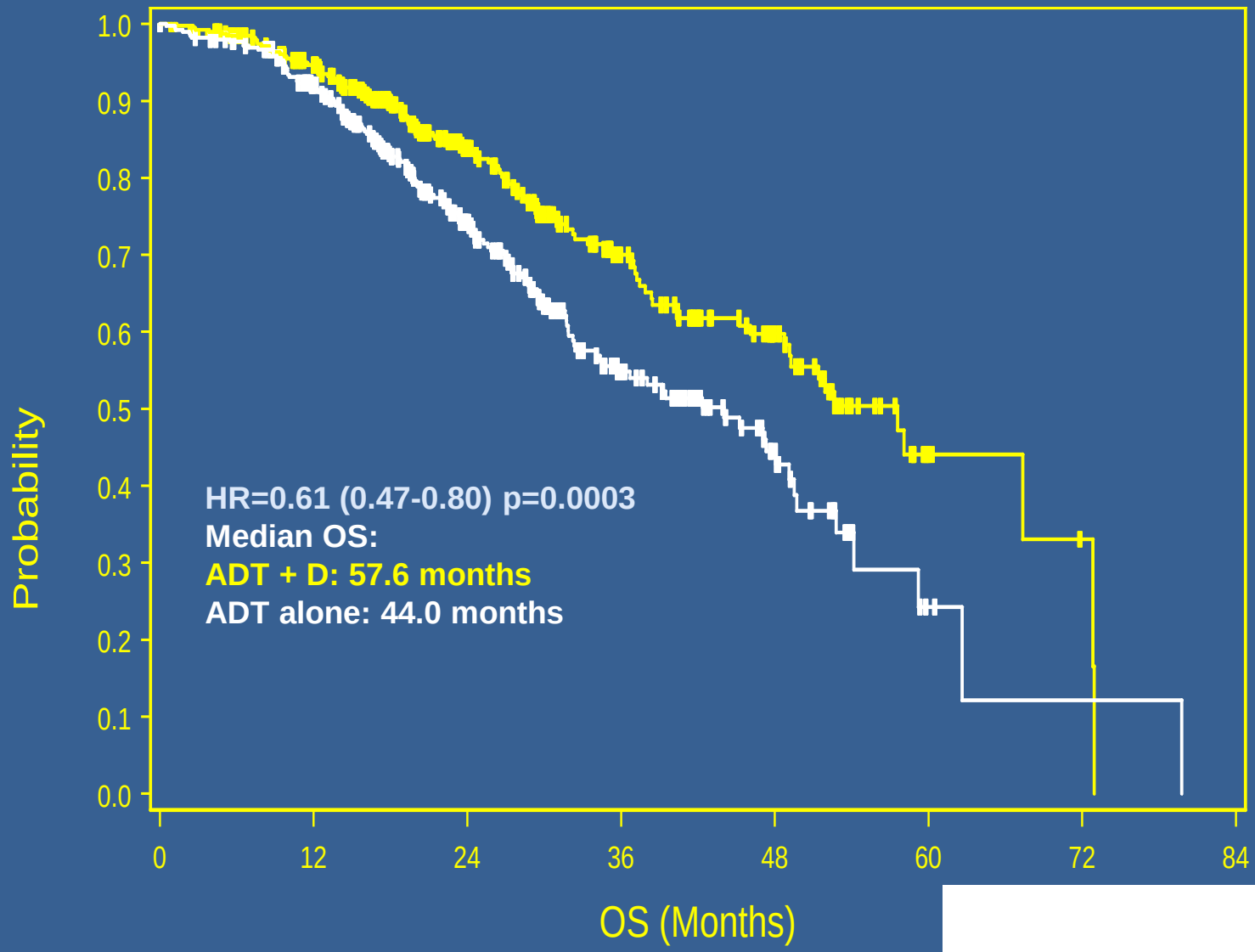
Now should be considered for patients with extensive disease at the initiation of androgen blockade

CHAARTED Trial: Is Earlier Use of Chemotherapy at Initiation of Androgen Blockade Beneficial for Patients With Extensive Disease?



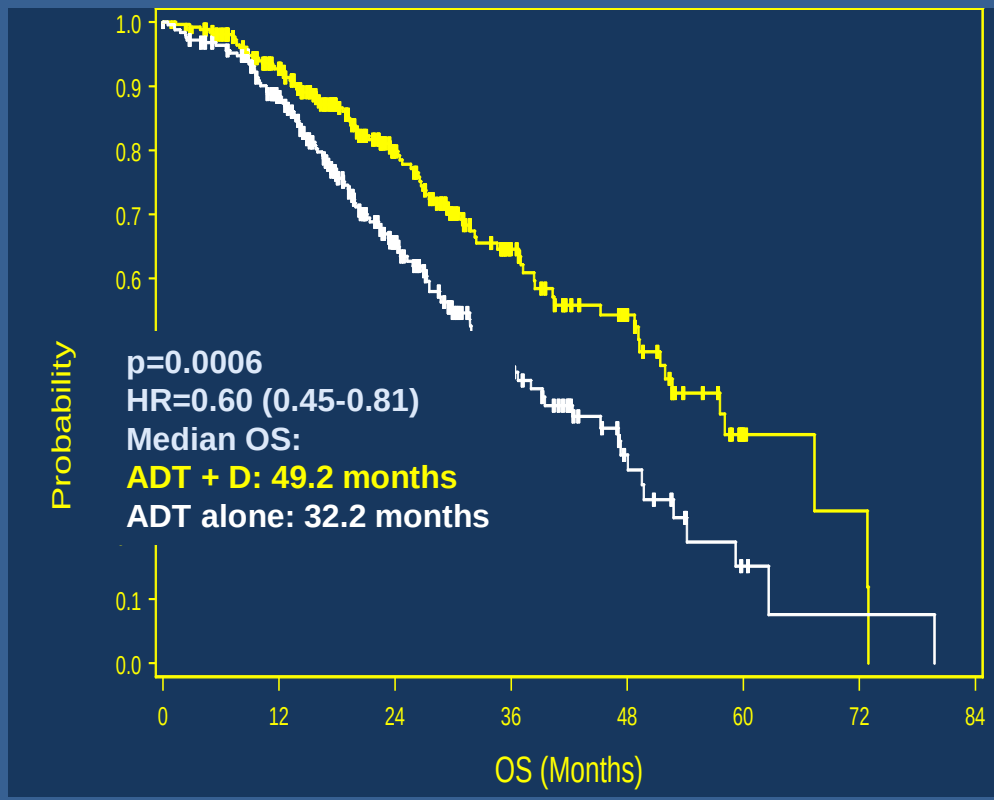
- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Primary endpoint: Overall survival

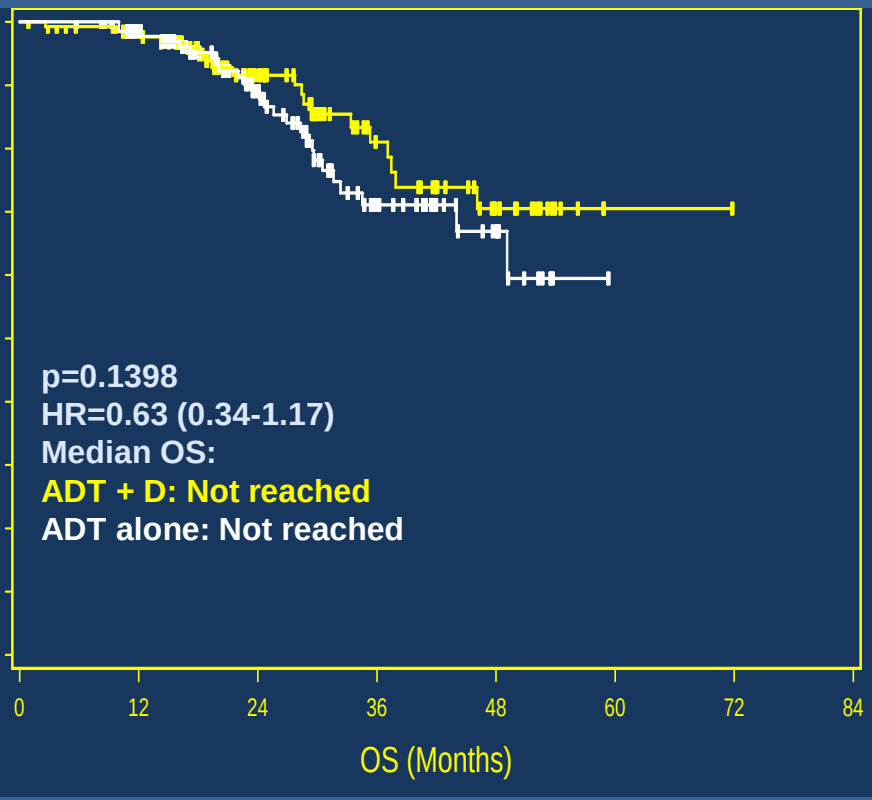


OS by extent of metastatic disease at start of ADT

High volume



Low volume



In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months

We projected 33 months in ADT alone arm with collaboration of SWOG9346 team

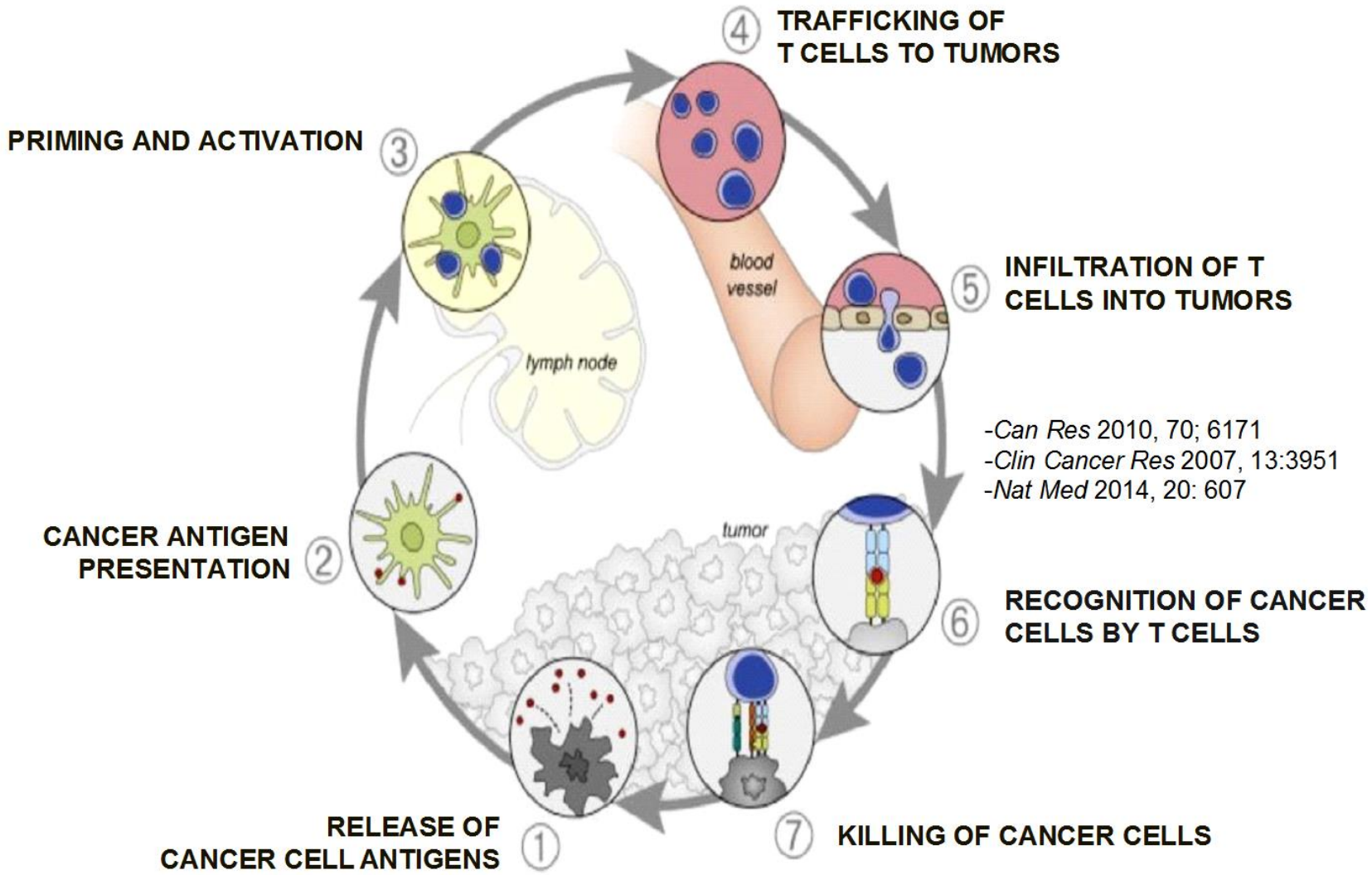
Clinical interpretation

- 6 cycles of docetaxel in addition to ADT represents an appropriate option for men with metastatic prostate cancer commencing ADT who are suitable for docetaxel therapy

- The benefit in patients with a high volume of metastases is clear and justifies the treatment burden
  - longer follow-up is required for patients with low volume metastatic disease

Immunotheraputic Treatment of Prostate Cancer

The Immunotherapy Cell Cycle



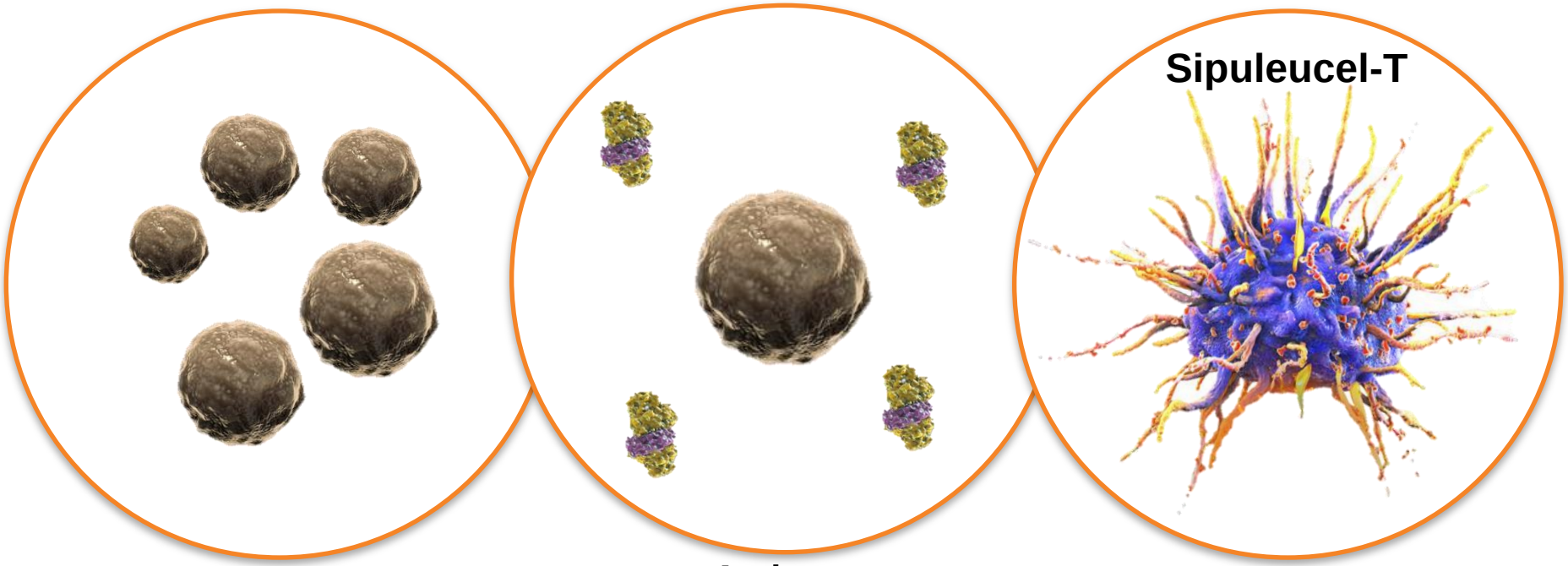
What Is Sipuleucel-T?

- An autologous cellular immunotherapy
- Derived from patient's own cells, stimulated ex vivo with a fusion peptide of PAP and GM-CSF (adjuvant)
- Sipuleucel-T is administered approximately every 2 weeks for a total of 3 infusions, with dosing completed in about 1 month
- First FDA-approved immunotherapy for mCRPC
- Indicated for men with asymptomatic or minimally symptomatic mCRPC

PAP=prostatic acid phosphatase; GM-CSF=granulocyte-macrophage colony-stimulating factor.

Sipuleucel-T Is Personalized Autologous Cellular Immunotherapy

Leukapheresis → **Sipuleucel-T Dose Manufactured** → **Personalized Sipuleucel-T Dose**



Patient's Immature APCs Collected (CD54+ cells)

Antigen Presentation to APC

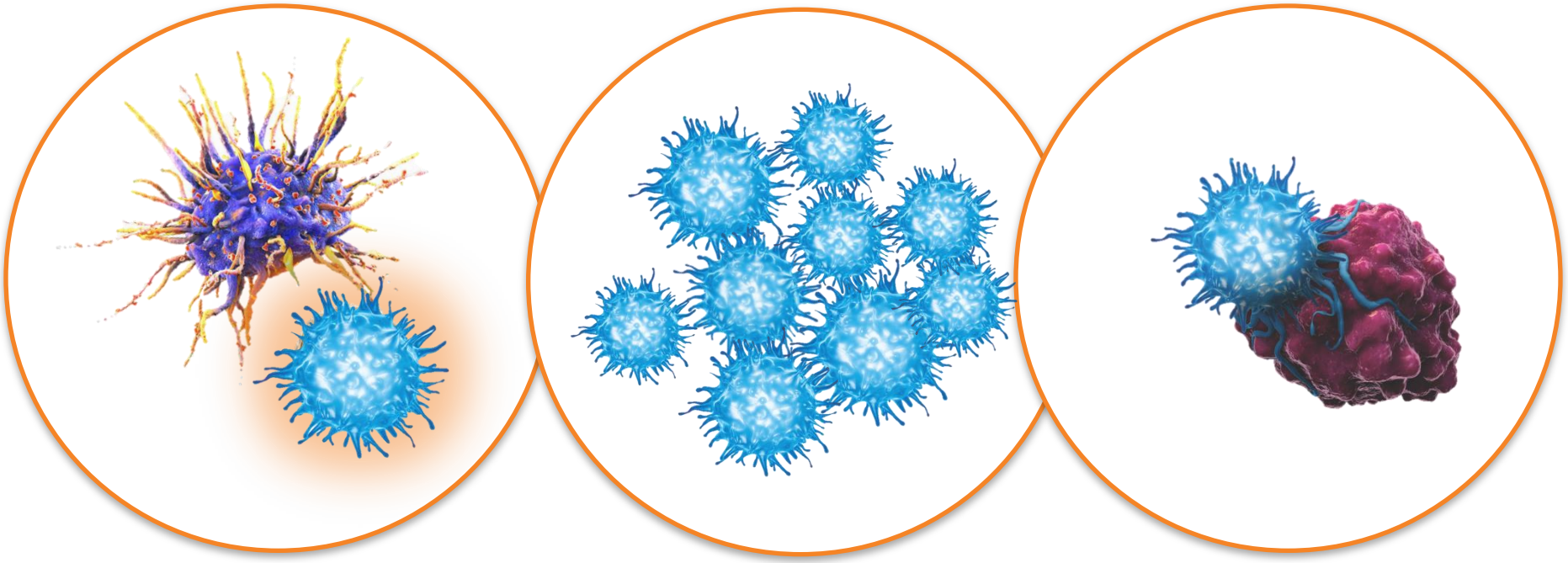
APC Maturation and Upregulation

APC=antigen-presenting cell.

Sharma P et al. *Nat Rev Cancer*. 2011;11:805-812.

Sipuleucel-T Activates Immune Cells to Stimulate a Response to Prostate Cancer

Personalized Dose Infused → **Immune Response Activation** → **Immune Response Mobilization**



Sipuleucel-T Activation of T Cells

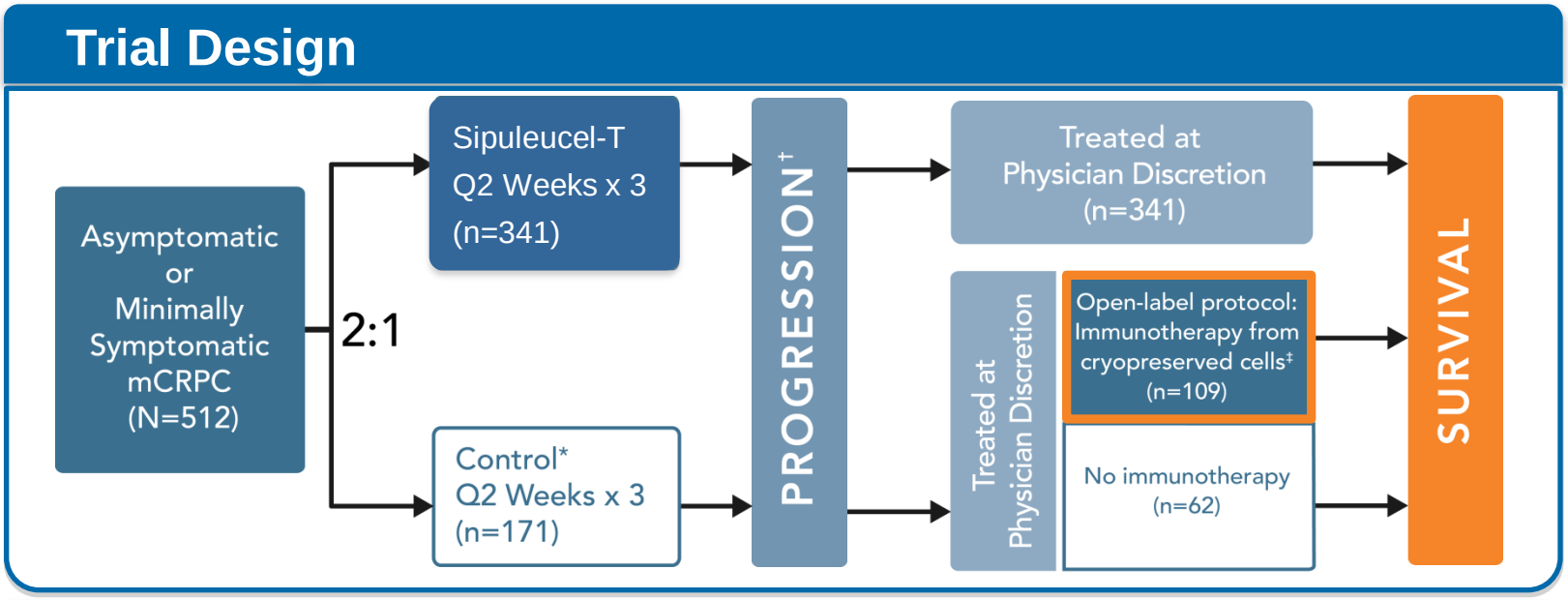
Activated T Cell Proliferation

Activated T Cells Attack Prostate Cancer

Sharma P et al. *Nat Rev Cancer*. 2011;11:805-812.

IMPACT Trial Design

- Phase 3, randomized, double-blind, controlled study
- Primary endpoint—overall survival



64% of patients in the control group, following progression, crossed over to a nonrandomized, open-label protocol

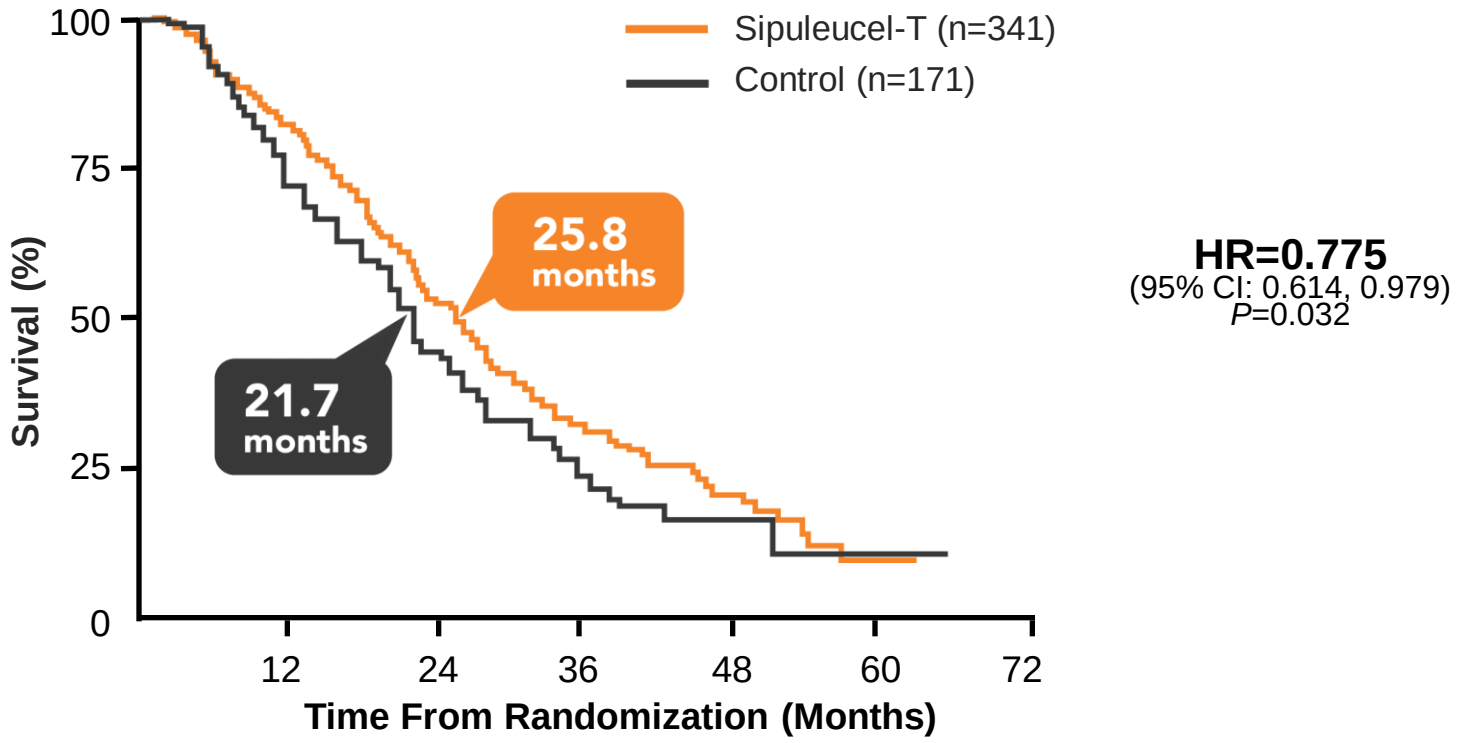
- They received investigational autologous immunotherapy made from cryopreserved cells
- Treatment in the open-label protocol was at the physician's discretion

*Control was nonactivated, autologous, peripheral blood mononuclear cells. †Progression=radiographic evidence of disease progression.
‡Autologous, peripheral blood mononuclear cells that were cryopreserved at the time of control generation and subsequently activated.

Kantoff PW et al. *N Engl J Med*. 2010;363:411-422.

Sipuleucel-T Extends Median Overall Survival (OS) Beyond 2 Years

Overall Survival Benefit of Sipuleucel-T

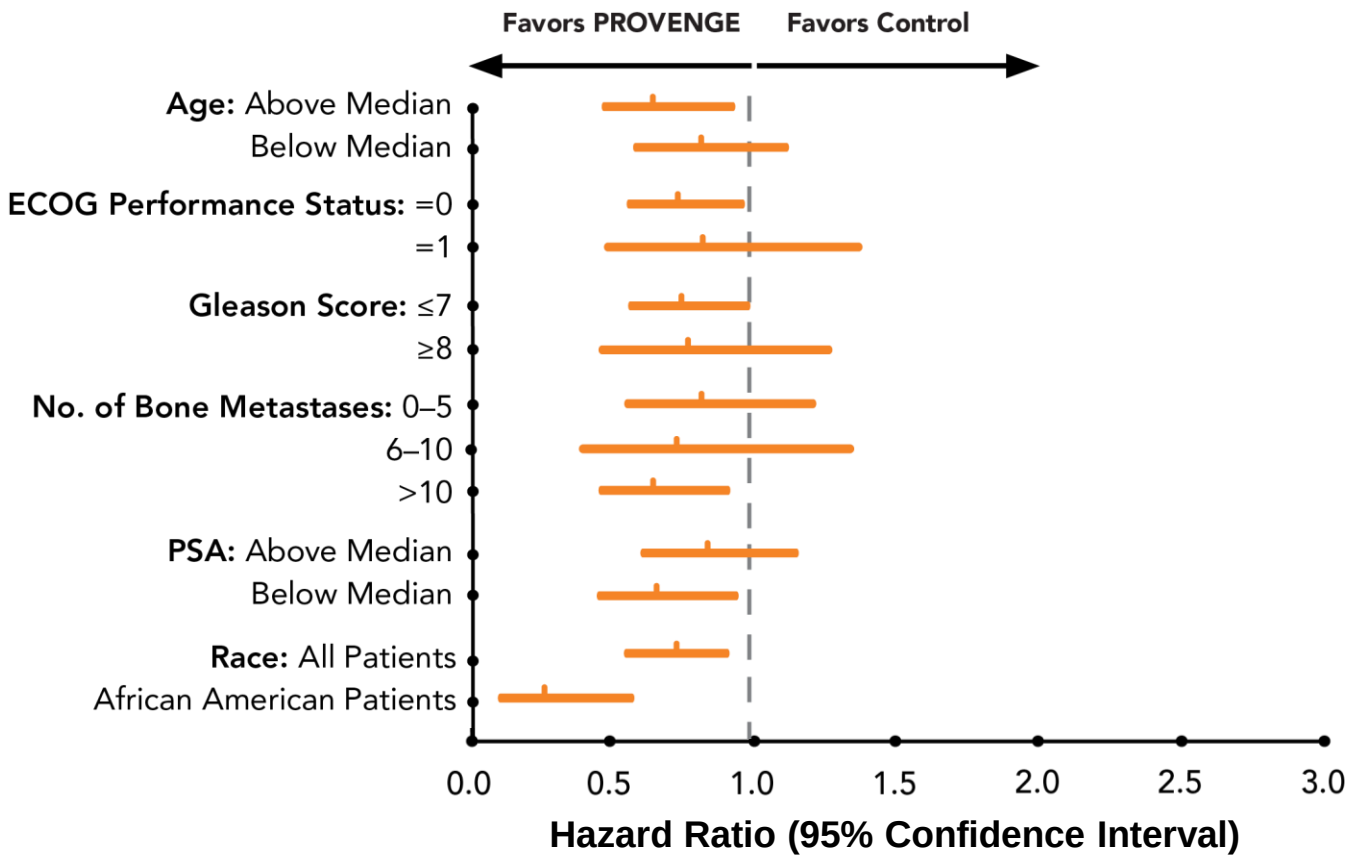


- 64% of patients in the control group crossed over to receive an investigational autologous immunotherapy made from cryopreserved cells
- Consistent survival benefit observed both with and without censoring for docetaxel after sipuleucel-T

Kantoff PW et al. *N Engl J Med*. 2010;363:411-422.

IMPACT: Survival Benefit Maintained Across Patient Subgroups Studied

Sipuleucel-T Subgroups of Interest



Kantoff PW et al. *N Engl J Med*. 2010;363:411-422.

Optimal timing for treatment of metastatic castration-resistant prostate cancer (mCRPC): sequencing and identifying parameters of early progression with sipuleucel-T

E. David Crawford, M.D.[1], Adam S. Kibel, M.D.[2], Neal D. Shore, M.D., F.A.C.S.[3]

[1]University of Colorado Anschutz Medical Campus, Aurora, Colorado; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Atlantic Urology Clinics, Myrtle Beach, SC

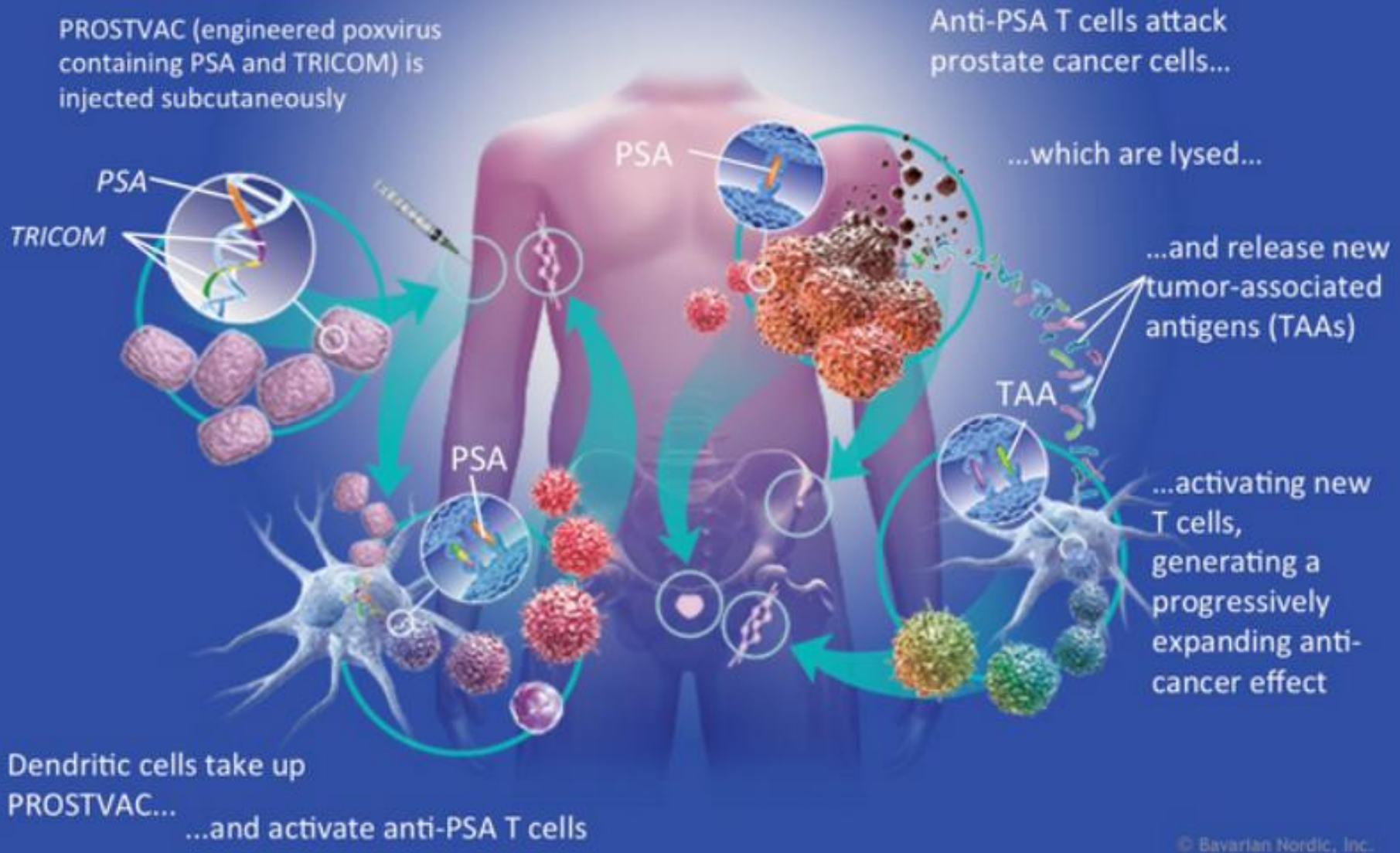
Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

Baseline PSA ng/mL	≤22.1 (n=128)	>22.1 to 50.1 (n=128)	>50.1 to 134.1 (n=128)	>134.1 (n=128)
Median OS, months				
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference, Difference, months	**13.0**	**7.1**	**5.4**	**2.8** 2.8
HR (95% CI)	0.51 (0.31 – 0.85)	0.74 (0.47 – 1.17)	0.81 (0.52 – 1.24)	0.84 (0.55 – 1.29)

- Although all PSA quartile groups in IMPACT showed a benefit from sipuleucel-T treatment, those in the lowest PSA quartile benefitted the most in terms of OS
- The magnitude of treatment effect in patients in the lowest quartile appeared to be greater than those in the highest quartile (13.0 vs. 2.8 months median OS benefit, respectively)

1. Crawford ED et al. AUA 2013. Abstract #960; 2. Schellhammer PF et al. *Urology*. 2013 Jun;81(6):1297-302

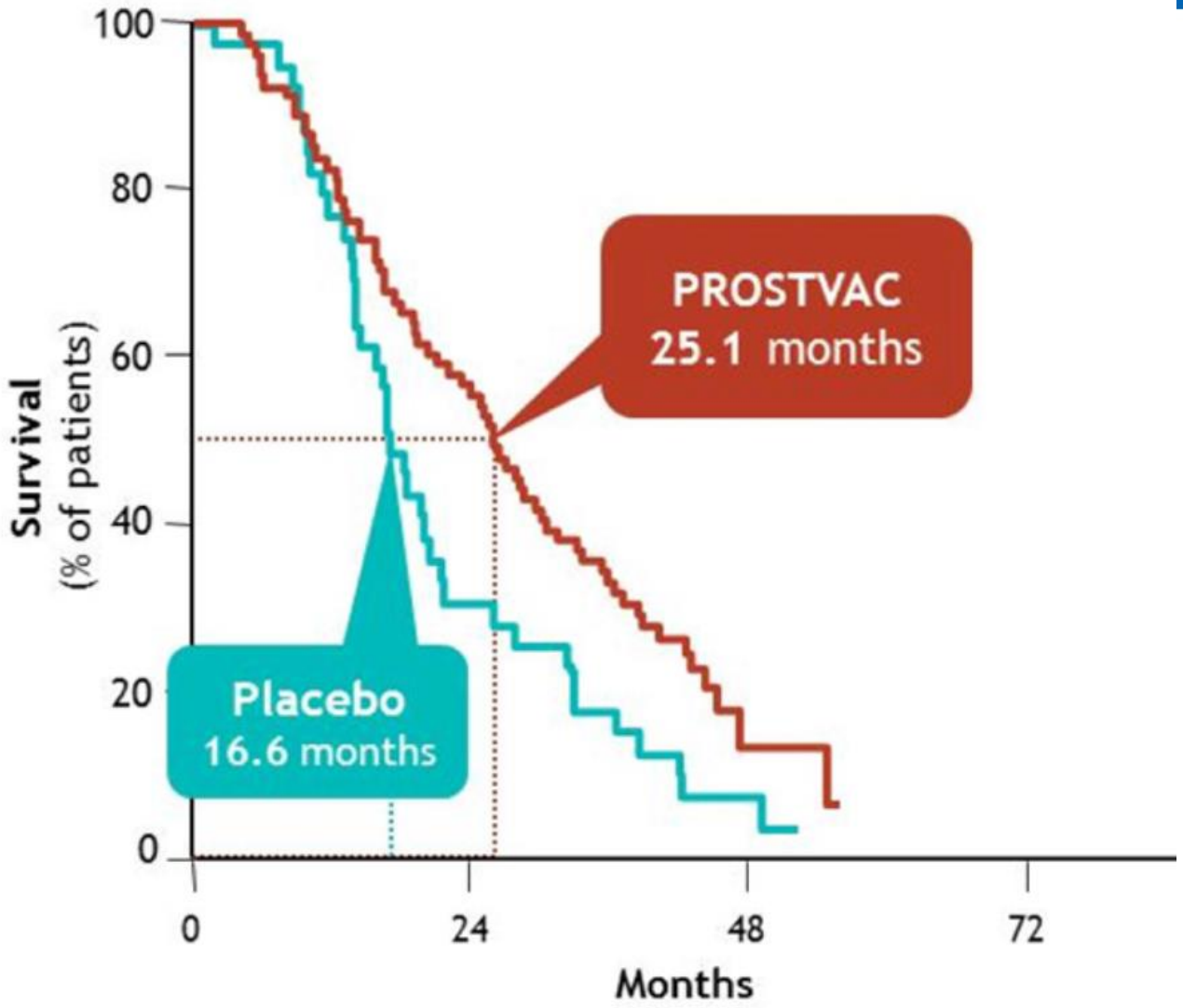
PROSTVAC May Trigger a Progressively Expanding, Specific Immune Response Against Prostate Cancer



PROSTVAC Monotherapy

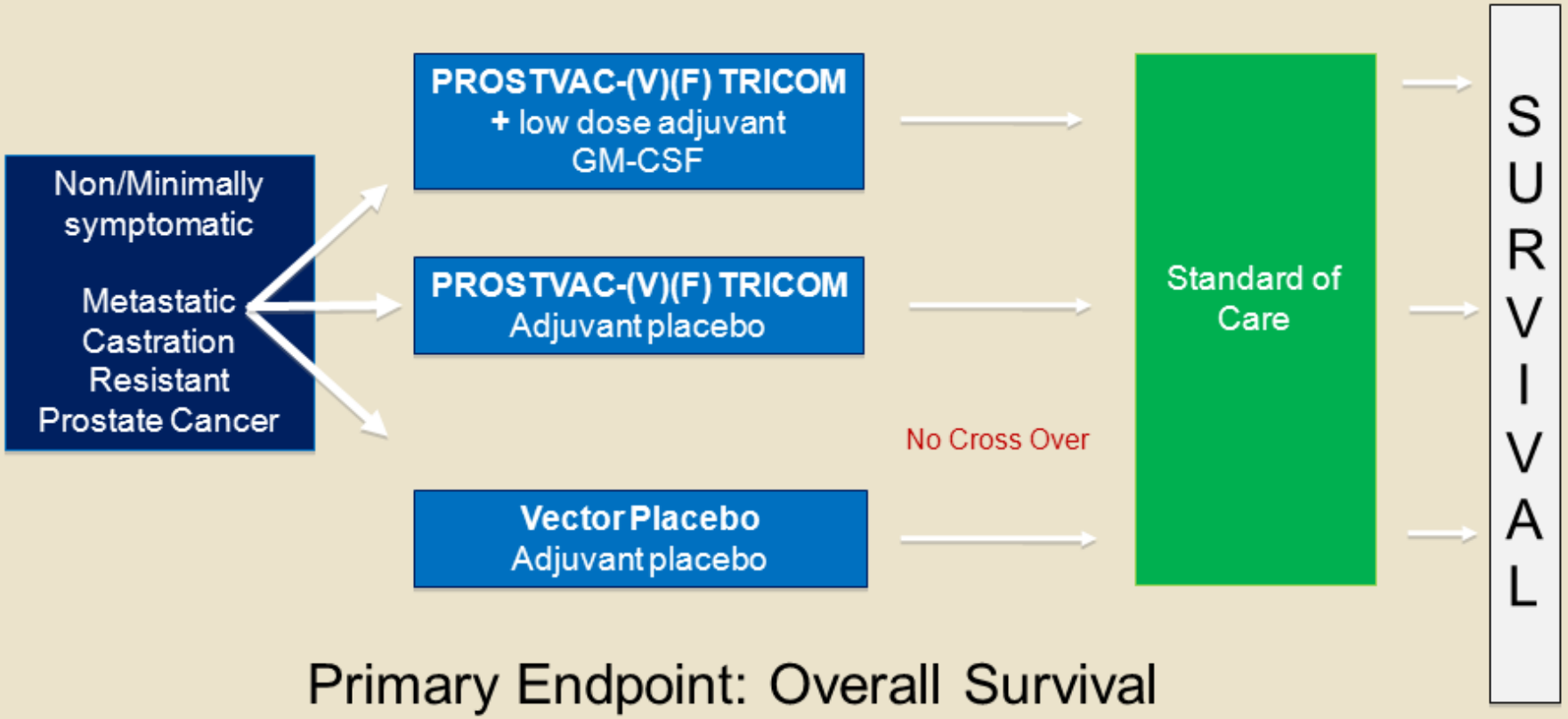
Phase 2 Study

Kantoff PW, et al. *J Clin. Oncol.* 2010; 28:1099-1105



PROSPECT Global Phase 3 Trial: Design (SPA)

(US-CAN-AUS/WE/EE/Latin America)



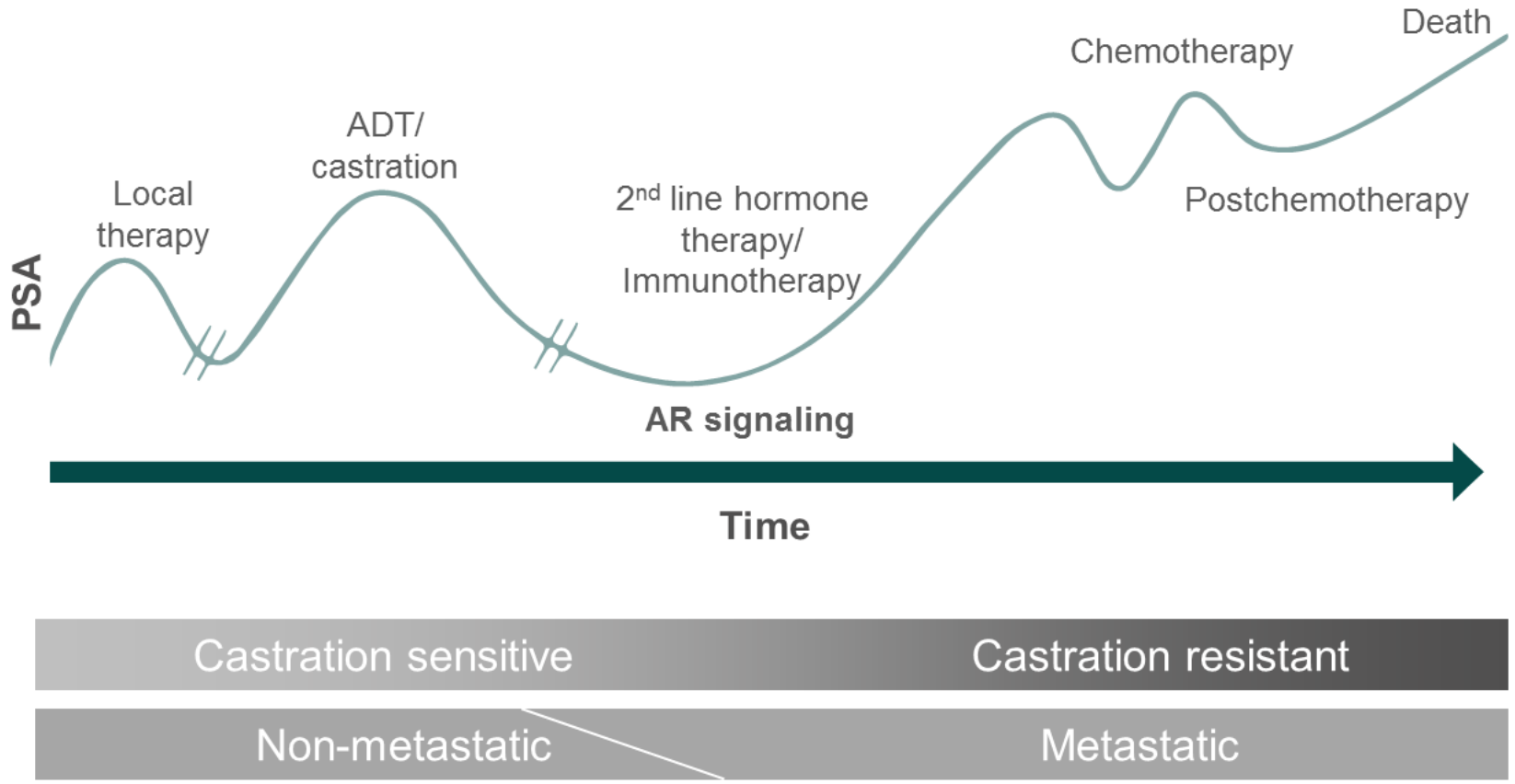
Primary Endpoint: Overall Survival

NATIONAL CANCER INSTITUTE

New Hormonal Therapies for Advanced Prostate Cancer

Prostate Cancer Remains Dependent on AR Signaling Throughout the Disease Continuum[1-6]

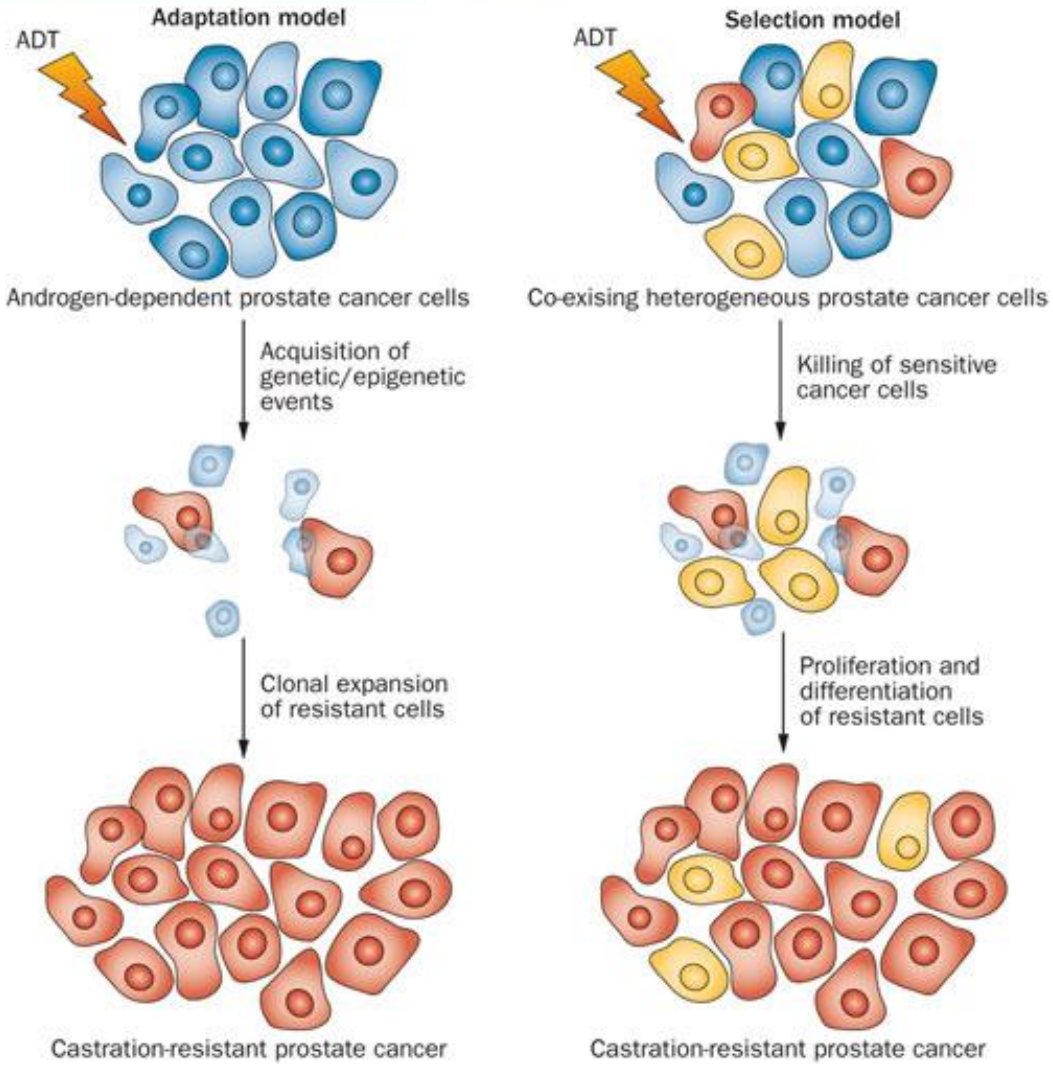
Treatment continuum based on historical data[a]



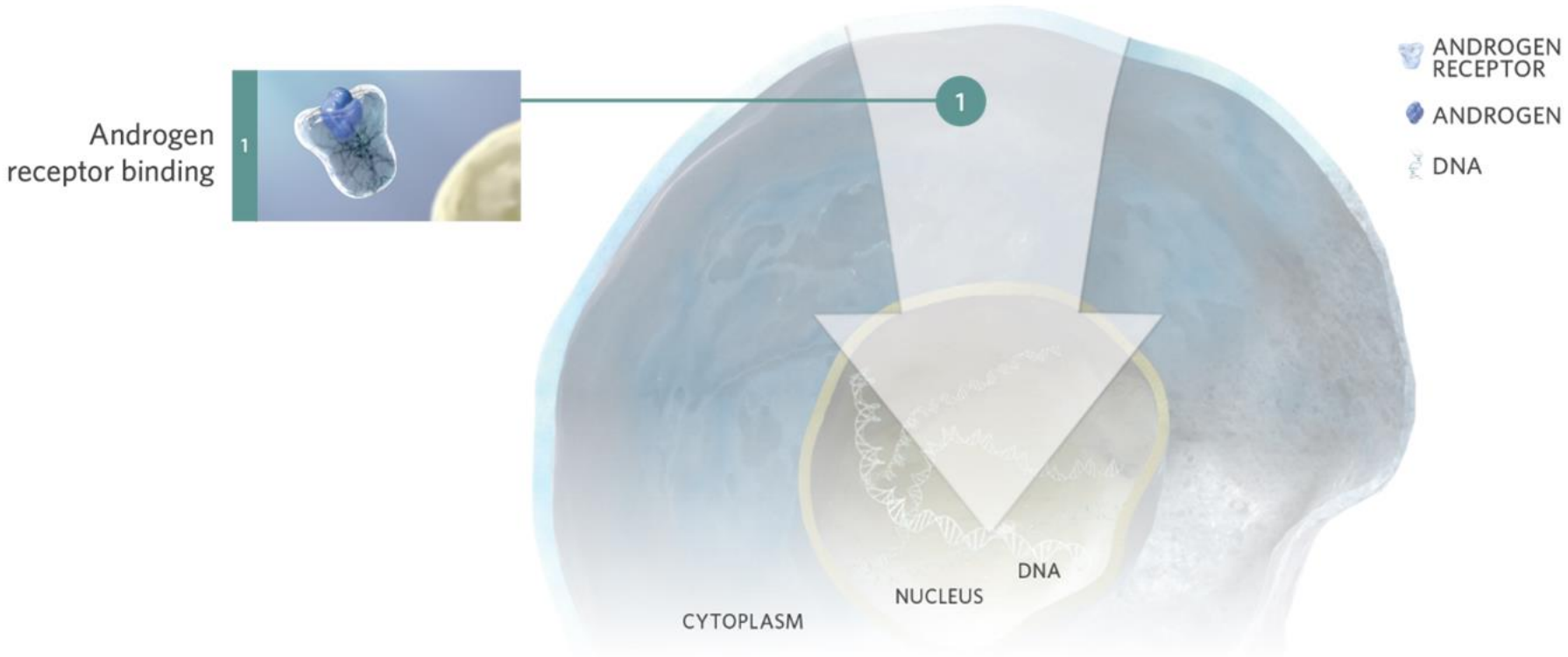
[a]The continuum is based on a historical paradigm and is not reflective of all currently available treatments.
ADT, androgen deprivation therapy; AR, androgen receptor.

1. Scher HI, et al. *J Clin Oncol.* 2008:26:1148-1159. **2.** Holzbeierlein J, et al. *Am J Pathol.* 2004;164:217-227. **3.** Attard G, et al. *Cancer Res.* 2009;69:2912-2918. **4.** Taplin ME, et al. *New Eng J Med.* 1995;332:1393-1398. **5.** Chen CD, et al. Nat Med. 2004;10:33-39. **6.** Linja MJ, et al. *Cancer Res.* 2001;61:3550-3555.

The Transition From Hormone Sensitive to Castration Resistant Prostate Cancer Adaption Model and Selection Model

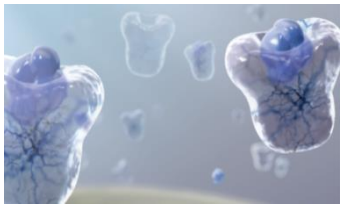


The AR Signaling Pathway is a Key Driver of Prostate Cancer Growth and Proliferation



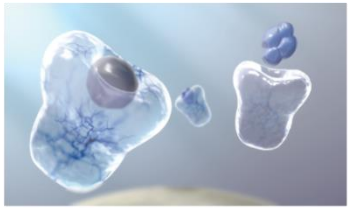
Holzbeierlein J, et al. *Am J Pathol*. 2004;164:217-227

Continued AR Signaling in CRPC is Driven Through Aberrant Mechanisms



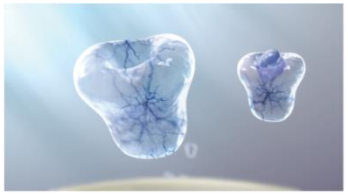
AR Overexpression

Result:
Overabundance of ARs, increasing the probability of androgen binding even at castrate levels of androgen[1-4]



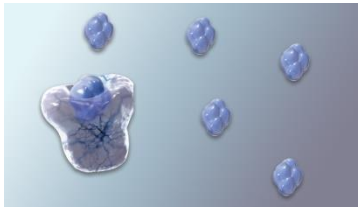
AR Promiscuity

Result:
ARs are activated by non-androgen ligands (eg, estrogen, progesterone, prednisone)[5-8]



Androgen-Independent Activation

Result:
ARs remain constitutively active without the need for androgen or non-androgen ligands[9-11]



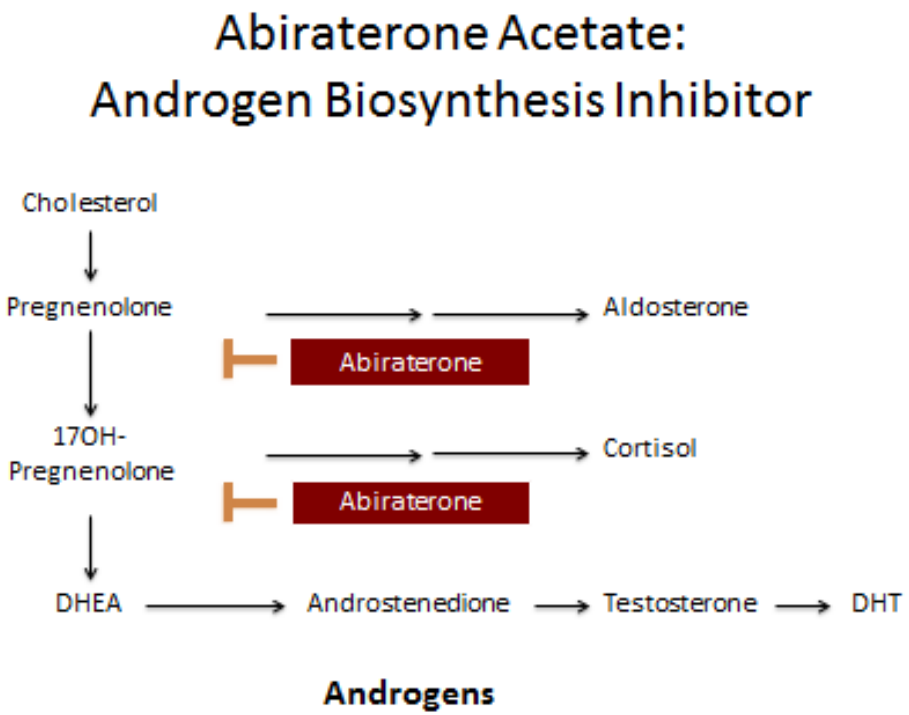
Intratumoral Production of Androgen

Result:
Tumor produce androgens that can bind to ARs despite castrate levels of androgen[12]

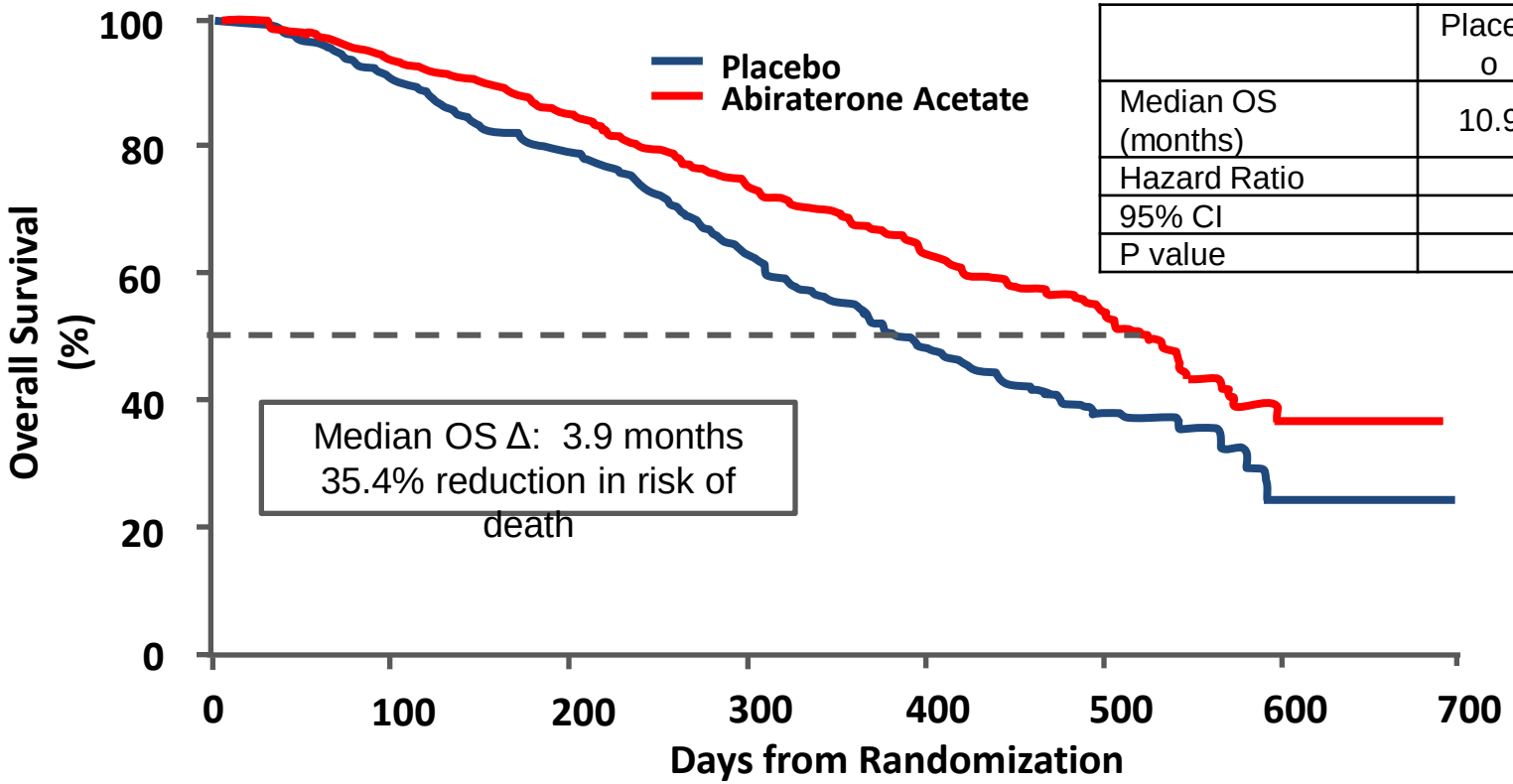
ANDROGEN RECEPTOR ANDROGEN NON-ANDROGEN

1. Linja MJ, et al. *Cancer Res*. 2001;61:3550-3555. **2.** Tran C, et al. *Science*. 2009;324:787-790. **3.** Bubendorf L, et al. *Cancer Res*. 1999;59:803-806. **4.** Koivisto P, et al. *Cancer Res*. 1997;57:314-319. **5.** Taplin ME, et al. *N Engl J Med*. 1995;332:1393-1398. **6.** Zhao XY, et al. *Nat Med*. 2000;6:703-706. **7.** Veldscholte J, et al. *Biochem Biophys Res Commun*. 1990;173:534-540. **8.** Richards J, et al. *Cancer Res*. 2012;72:2176-2182. **9.** Hu R, et al. *Cancer Res*. 2009;69:16-22. **10.** Libertini SJ, et al. *Cancer Res*. 2007;67:9001-9005. **11.** Dehm SM, et al. *Cancer Res*. 2008;68:5469-5477. **12.** Knuutila M, et al. *Am J Pathol*. 2014;184:2163-2173

CRPC Tumors Produce their own Androgens that Bind to and Activate AR



COU 301: Abiraterone Prolonged Overall Survival in CRPC Patients Who Received Prior Chemotherapy



	Placebo	Abiraterone Acetate
Median OS (months)	10.9	14.8
Hazard Ratio	0.65	
95% CI	0.54-0.77	
P value	<0.001	

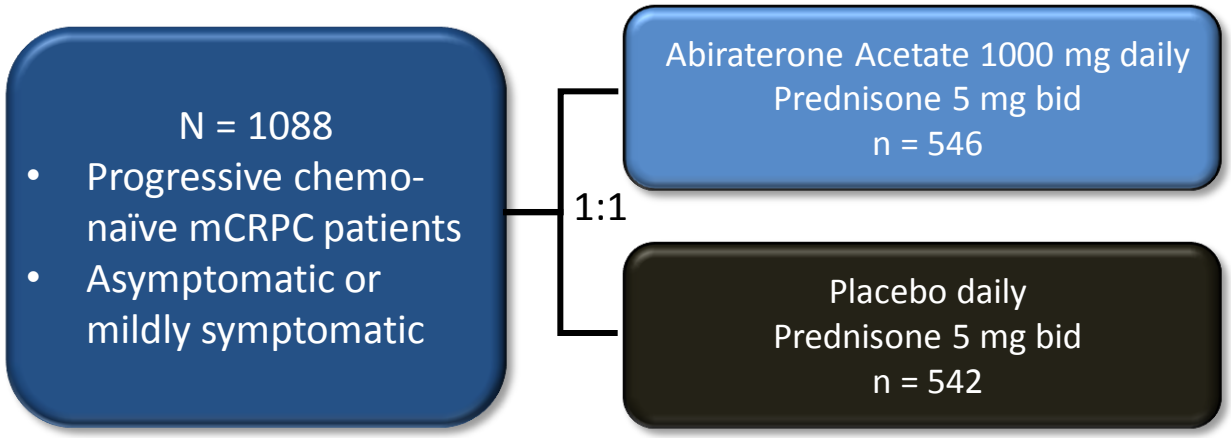
2 prior chemo OS: 14.0 months abiraterone acetate vs 10.3 months placebo[1]

1 prior chemo OS: 15.4 months abiraterone acetate vs 11.5 months placebo[1]

Updated results: 4.6-month difference in median survival with abiraterone acetate[2]

1. de Bono JS, et al. *N Engl J Med.* 2011;364(21):1995-2005. 2. Fizazi K, et al. European Multidisciplinary Cancer Congress; 2011. Abstract 7000.

COU 302: Abiraterone Acetate Phase III Trial in Chemo-naïve mCRPC



Primary Endpoints:

- Radiographic progression-free survival (rPFS) by central review
- OS

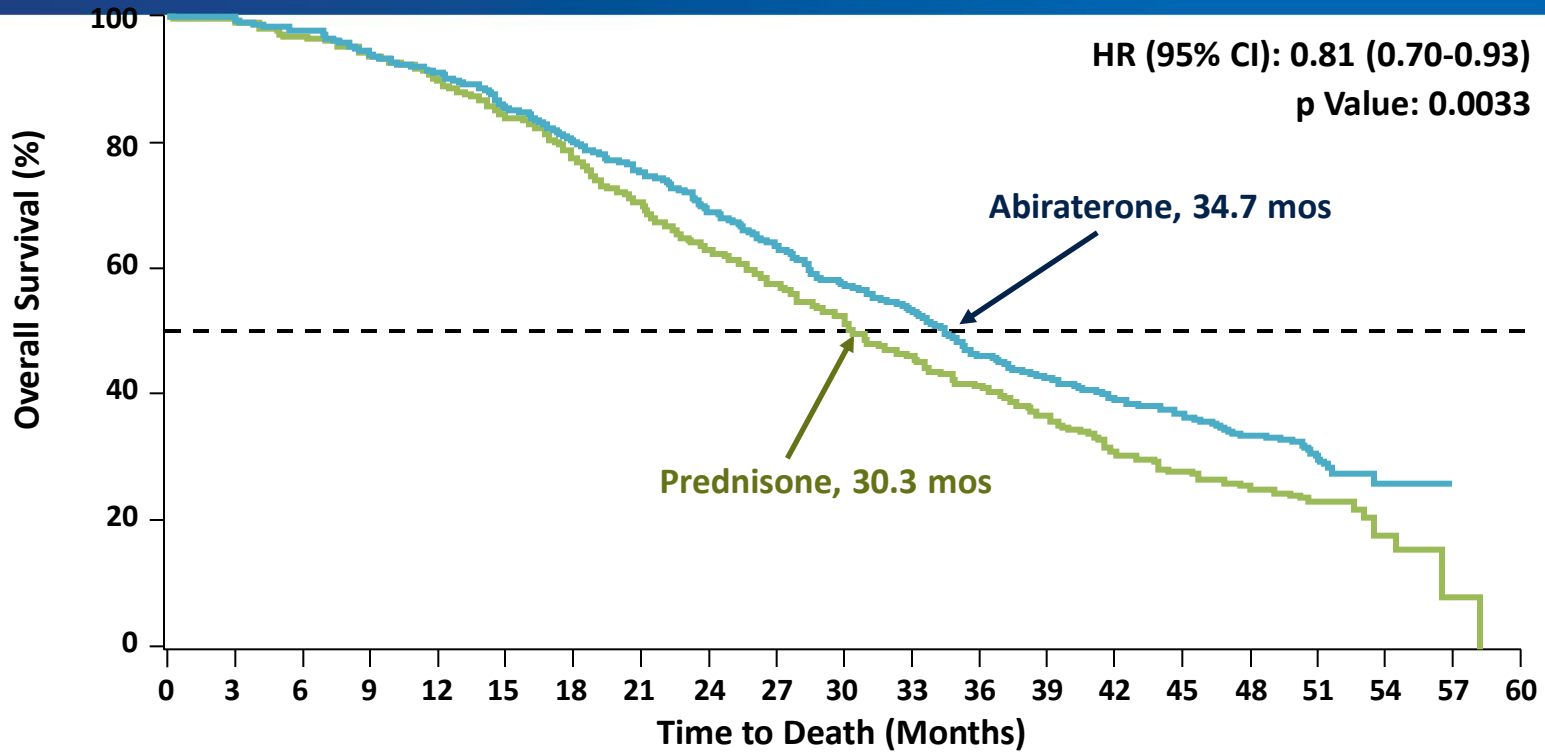
Secondary:

- Time to opiate use (cancer-related pain)
- Time to initiation of chemotherapy
- Time to ECOG PS deterioration
- Time to PSA progression

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

Saad F, et al. AUA 2013. Abstract 713

COU-AA-302, Final Overall Survival Analysis of a Randomized Phase 3 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Without Prior Chemotherapy



Abiraterone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

- Median follow-up of 49.2 mos
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

COU-302: Staistically-significant improvement in Secondary Endpoints for Abiraterone Treated Patients vs Placebo

Outcome	AA + Prednisone Median (months)	Placebo + Prednisone Median (months)	HR (95% CI)	P Value
rPFS	16.5	8.3	0.53 (0.45, 0.62)	< 0.0001
OS	35.3	30.1	0.79 (0.66, 0.96)	0.0151 *
Time to opiate use (cancer related pain)	Not reached	23.7	0.71 (0.59, 0.85)	0.0002
Time to chemotherapy initiation	26.5	16.8	0.61 (0.51, 0.72)	< 0.0001
Time to ECOG PS deterioration	12.3	10.9	0.83 (0.72, 0.94)	0.0052
Time to PSA progression	11.1	5.6	0.58 (0.43, 0.78)	< 0.0001

Patient reported outcomes favored AA + prednisone vs placebo + prednisone

Full data to be reported

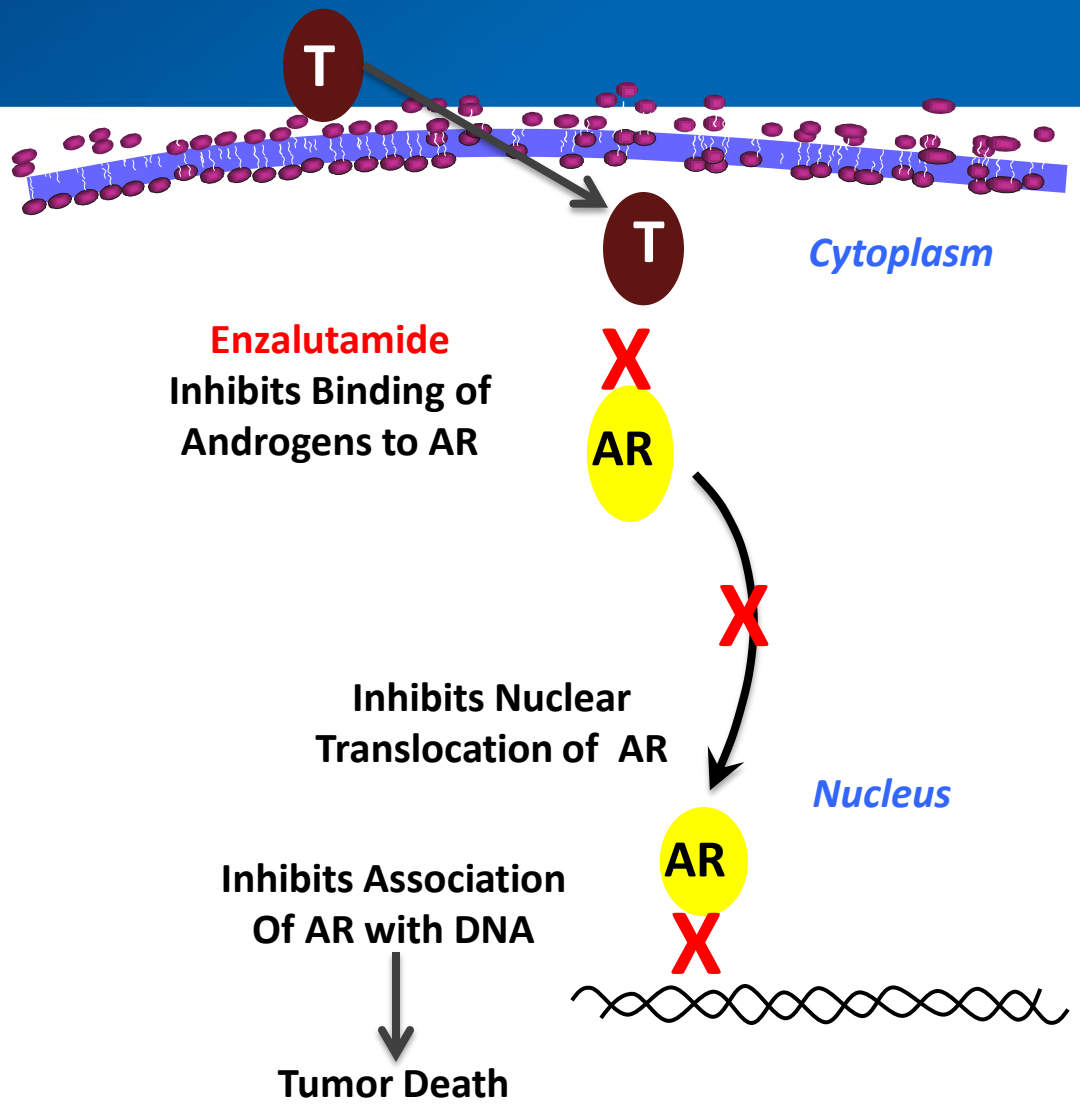
*Pre-specified alpha level 0.0035

Note: All secondary end points remain significant after adjusting for multiplicity testing

Saad F, et al. AUA 2013. Abstract 713

Enzalutamide – An Androgen Receptor Signal Inhibitor

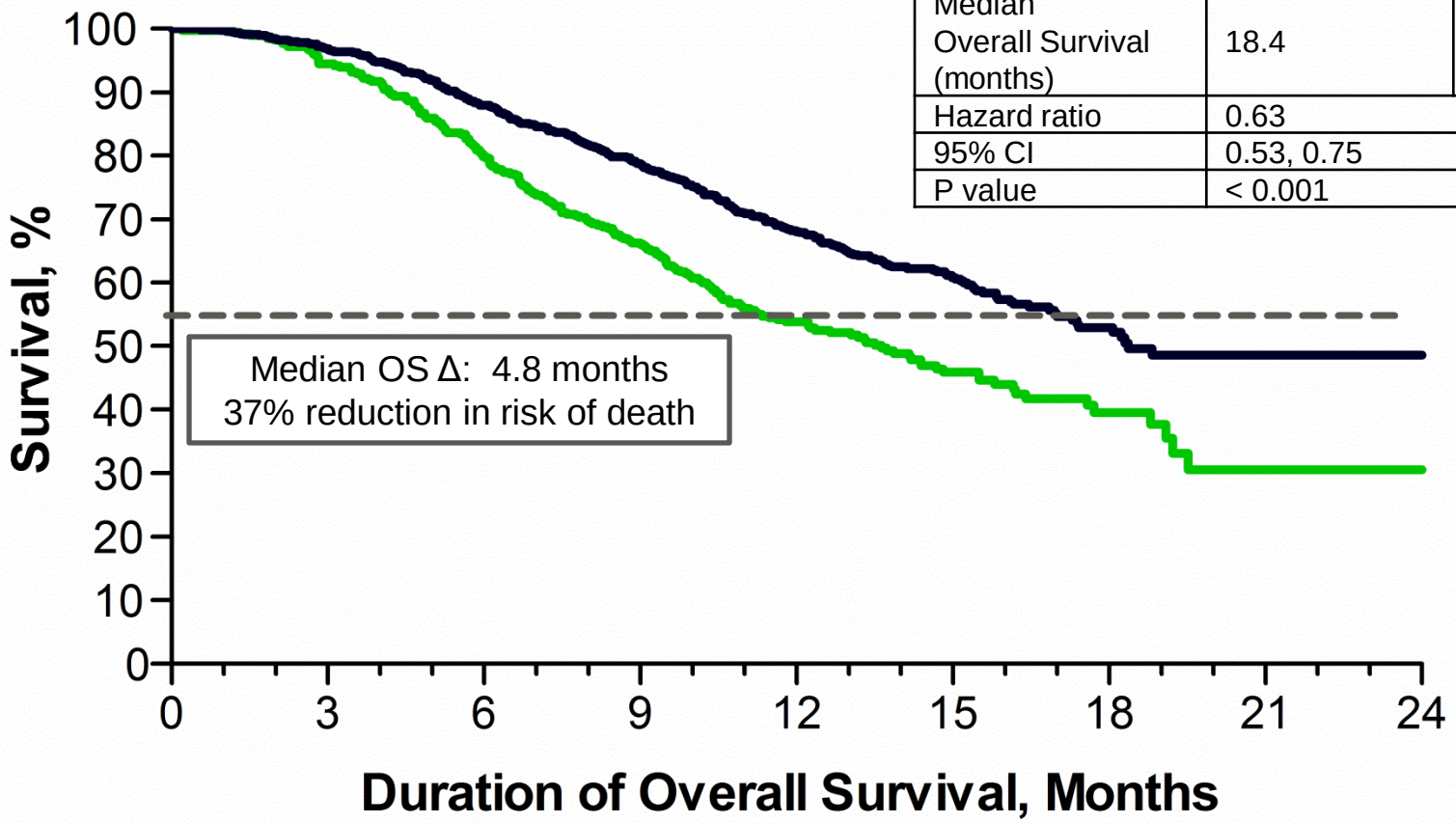
- Oral drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway
- No demonstrated agonist effects in pre-clinical models



Tran C et al. *Science* 2009;324:787-790.

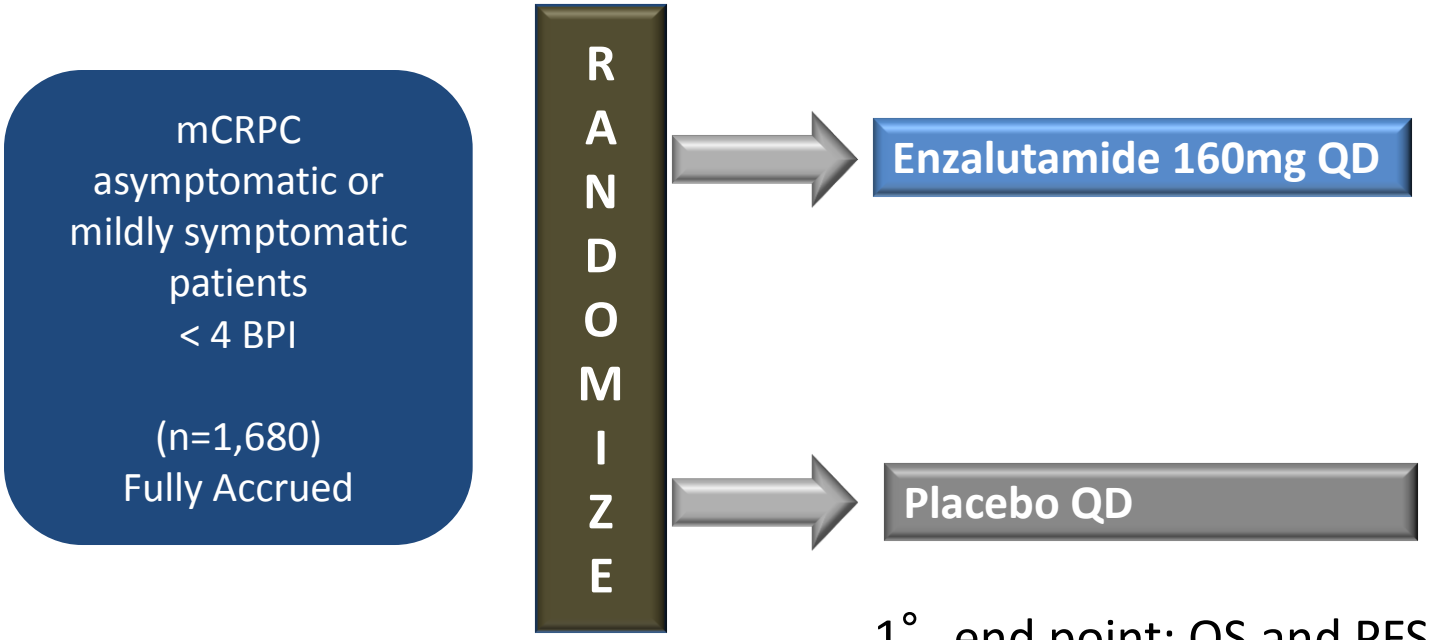
AFFIRM Trial: Enzalutamide Prolonged Survival, Reducing Risk of Death in Patients Previously Treated with Chemotherapy

	Enzalutamide	Placebo
Median Overall Survival (months)	18.4	13.6
Hazard ratio	0.63	
95% CI	0.53, 0.75	
P value	< 0.001	



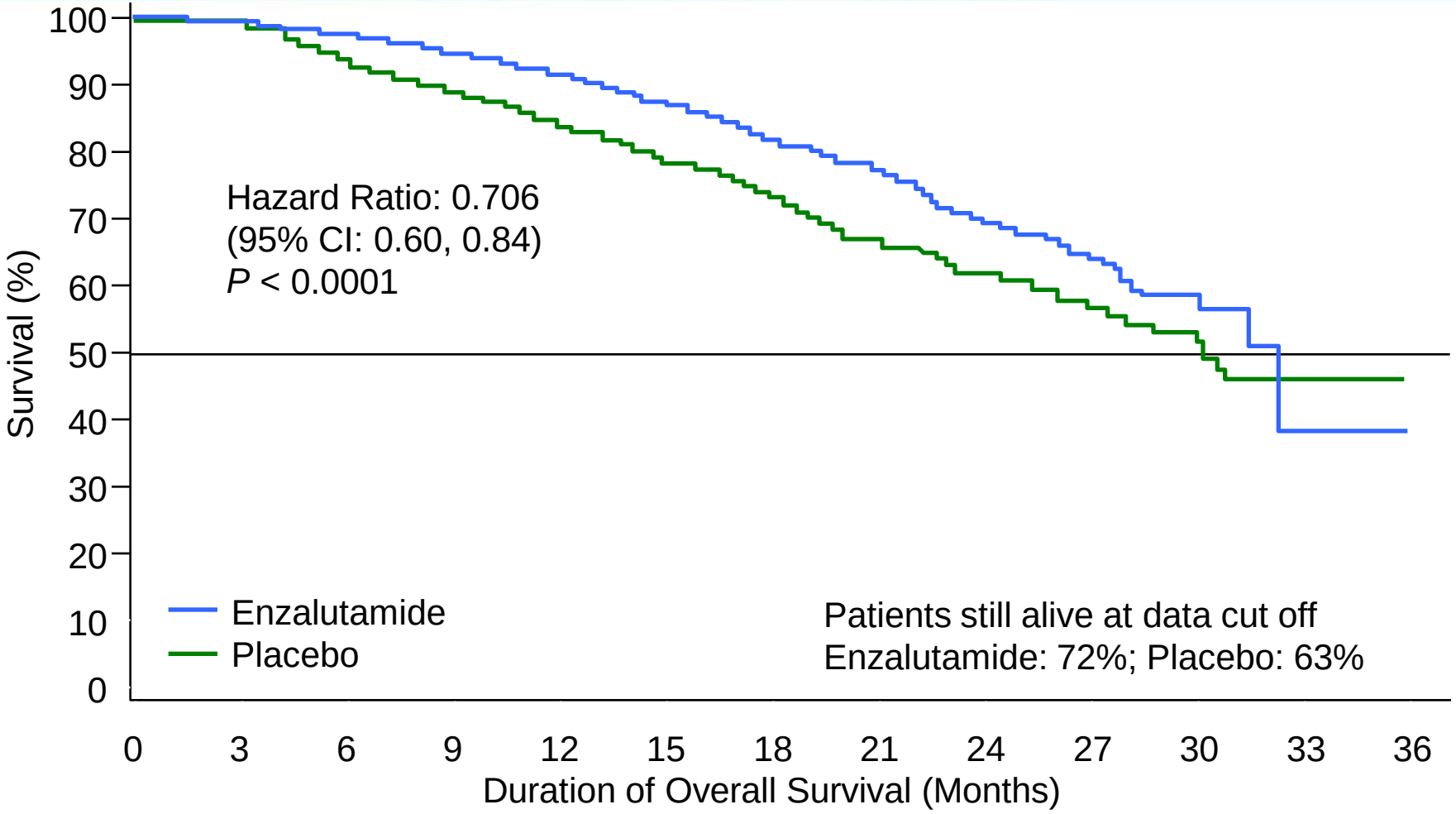
Scher HI, et al. *N Engl J Med.* 2013; 367:1187-1197

PREVAIL Phase III Trial of Enzalutamide in Asymptomatic or Mildly Symptomatic mCRPC Pre Chemotherapy



A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL) (NCT01212991). Available at www.clinicaltrials.gov. Accessed August 21, 2013.

PREVAIL: Phase III Trial of Ezalutamide in Asymptomatic or Mildly Symptomatic mCRPC Patients Pre-Chemotherapy -- OS



Median OS: Enzalutamide, 32.4 Months; Placebo, 30.2 months

Measuring Progression Can Be Problematic on Bone Scan

- MDP-mTc^{99} images osteoblast activity, not prostate cancer directly
- Lesion healing may appear new or more intense over time, particularly with newer hormonal therapies (ie, abiraterone)
- New lesions are best measures of progression vs flare (within clinical context)
- Confirmation scans showing additional new lesions required
- Misclassification is common with older criteria

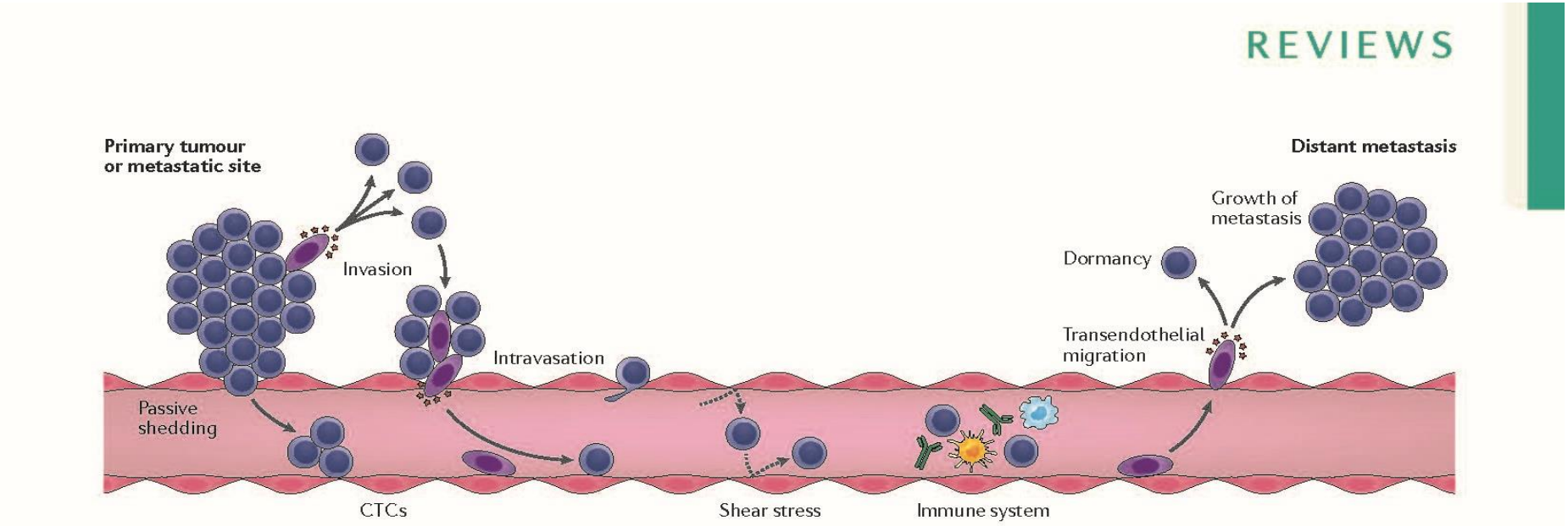
Thus, PCWG2 guidelines have redefined bone scan progression

  - Unknown if bone scan flare occurs with immunotherapy

Even-Sapir E et al. *J Nucl Med*. 2006;47:287-297; Scher HI et al. *J Clin Oncol*. 2008;26:1148-1159; Ryan CJ et al. *Clin Cancer Res*. 2011;17:1-8.

Schematic Representation of CTCs Entering the Peripheral Circulation and Establishing a Metastatic Focus at a Distant Site

MA Goron Nature Reviews/Urology, November 2016



Potential Clinical Applications for Circulating Tumor Cell Analysis

1. Early cancer detection
2. Disease staging
3. Monitoring for recurrence
4. Prognostication
5. Aid in selection of therapy

   Predict which CRPC patients are more likely to respond to androgen-receptor targeted therapies

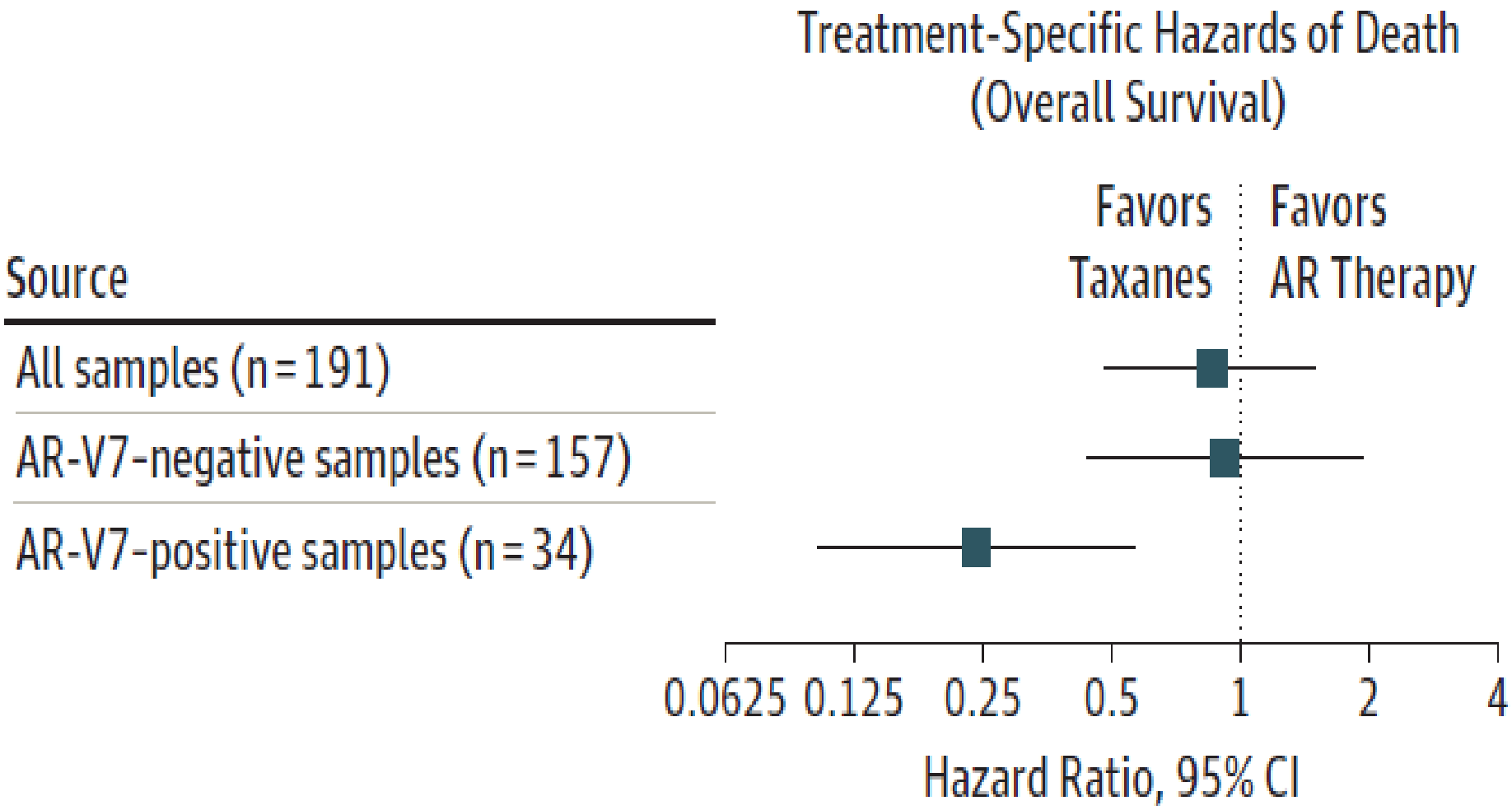
Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

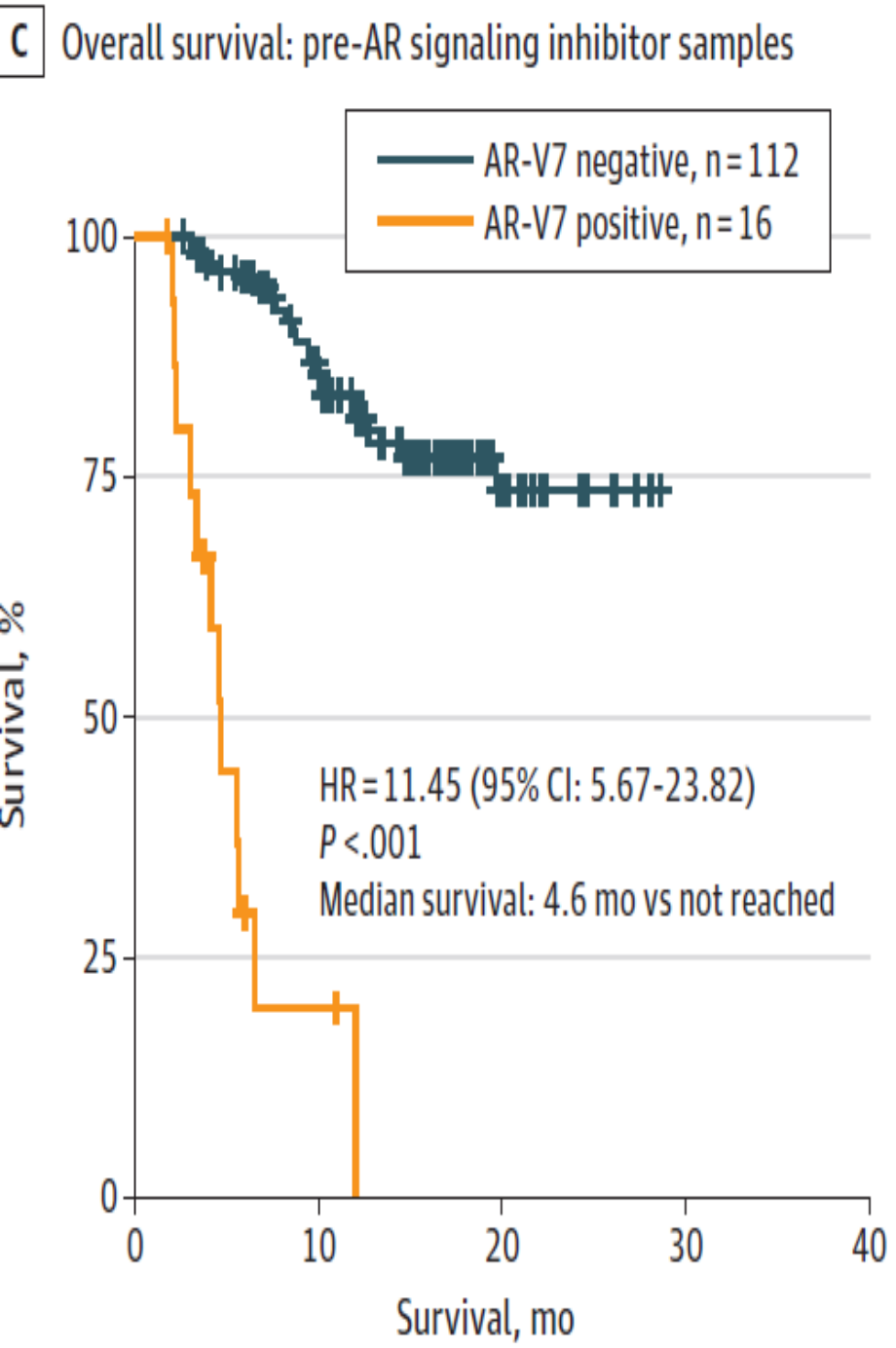
Howard I. Scher, MD; David Lu, PhD; Nicole A. Schreiber, BA; Jessica Louw, BS; Ryon P. Graf, PhD;Hebert A. Vargas, MD; Ann Johnson, MS; Adam Jendrisak, MBA; Richard Bambury, MB, BCh, BAO;Daniel Danila, MD; Brigit McLaughlin, BS; JustinWahl, BS; Stephanie B. Greene, PhD; Glenn Heller, PhD; Dena Marrinucci, PhD; Martin Fleisher, PhD; Ryan Dittamore, MBA

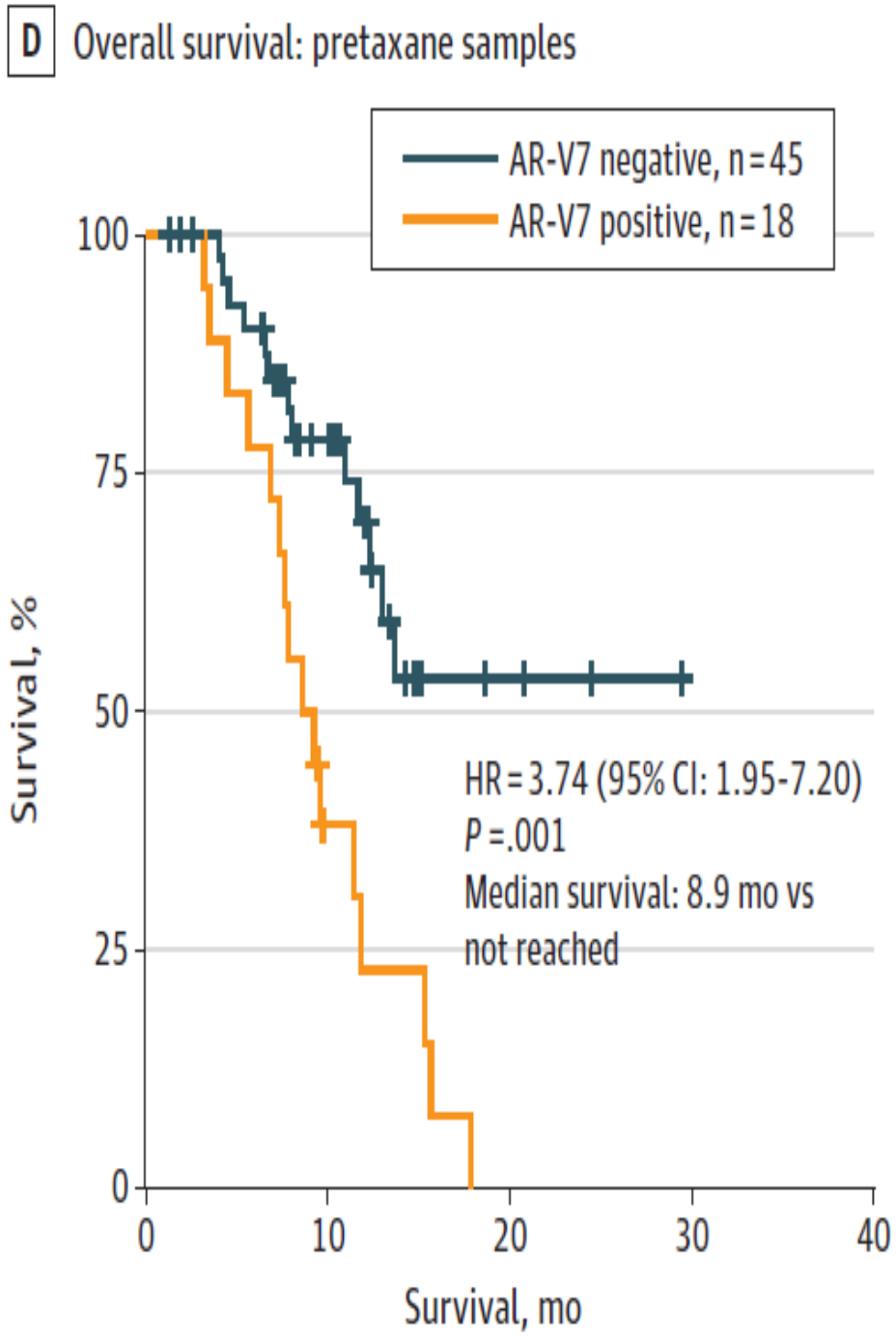
AR-V7 Expression in CTCs and CRPC Outcomes – Key Results

- mCRPC patients with pre-androgen receptor signaling (ARS) inhibitor AR-V7-positive CTCs had
  - Resistant PSA responses
  - Shorter time on therapy
  - Shorter radiographic progression-free survival
  - Inferior overall survival
  - Shows significant interaction with taxane administration

Figure 4. Patients With Pretherapy AR-V7-Positive CTCs and Overall Survival on Taxanes and/or AR Signaling Inhibitors.




C
Overall survival: pre-AR signaling inhibitor samples
AR-V7 negative, n = 112
AR-V7 positive, n = 16
100
75
50
25
0
Survival, %
HR = 11.45 (95% CI: 5.67-23.82)
P <.001
Median survival: 4.6 mo vs not reached
0
10
20
30
40
Survival, mo


D
Overall survival: pretaxane samples
AR-V7 negative, n = 45
AR-V7 positive, n = 18
100
75
50
25
0
Survival, %
HR = 3.74 (95% CI: 1.95-7.20)
P =.001
Median survival: 8.9 mo vs not reached
0
10
20
30
40
Survival, mo

New and Novel Treatment Strategies

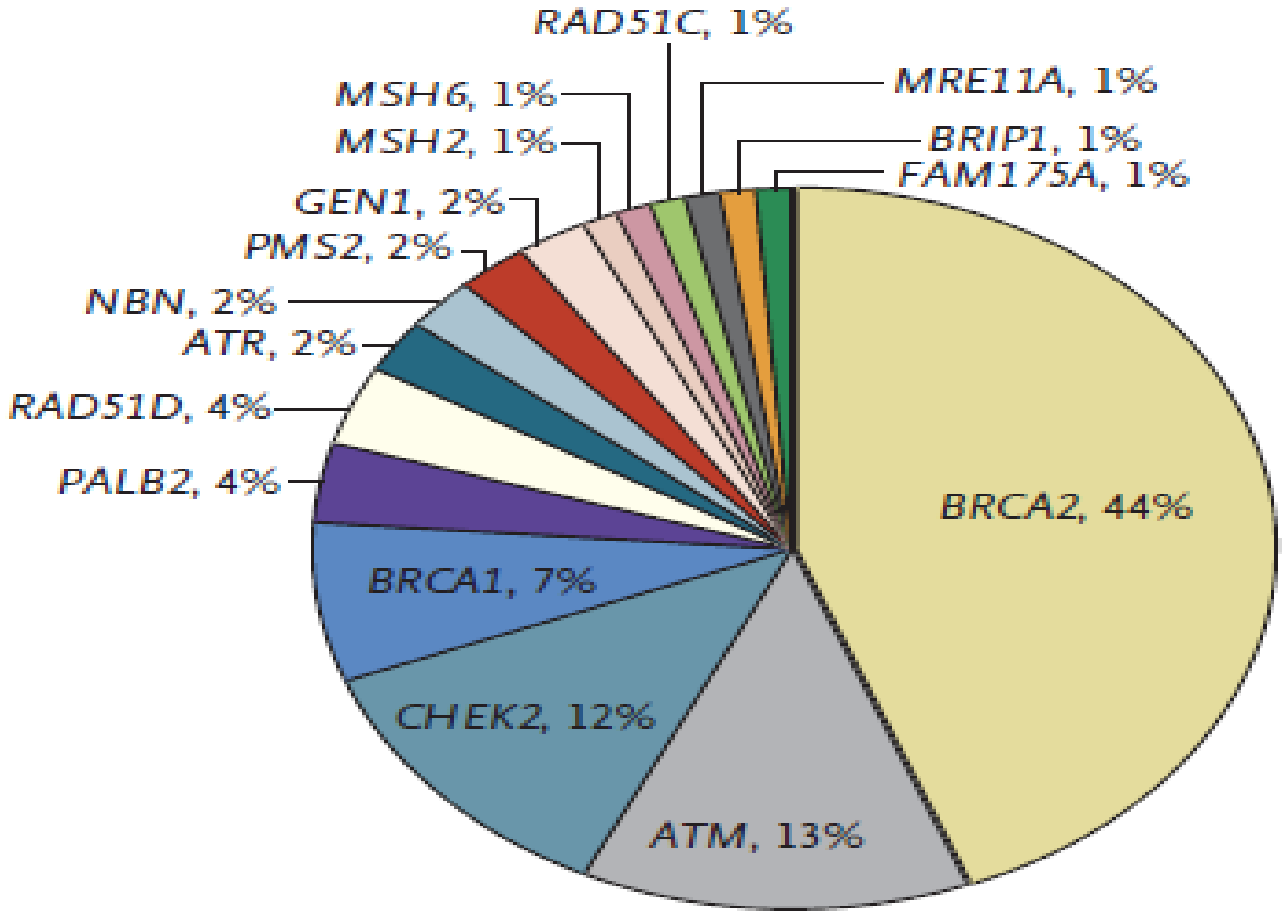
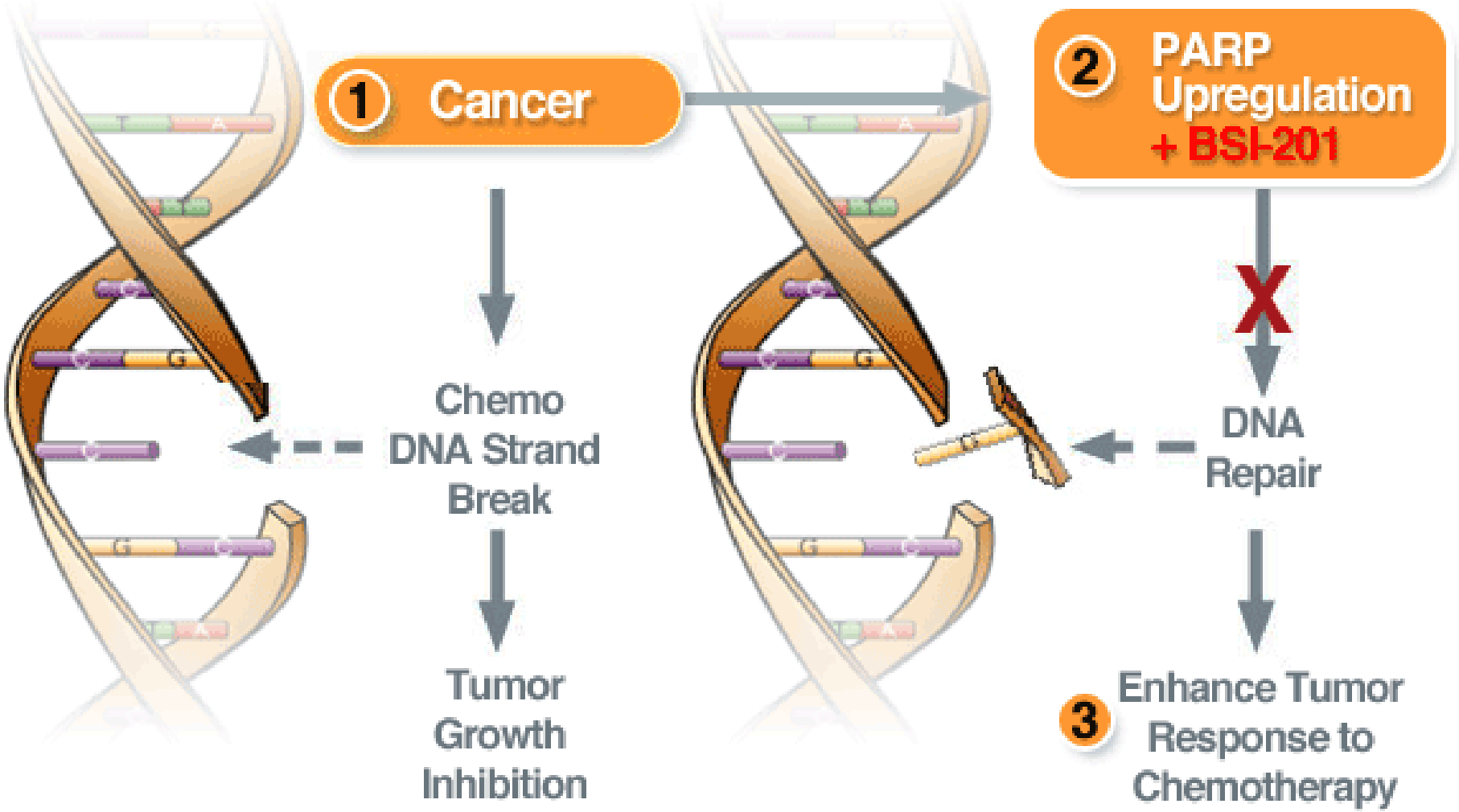


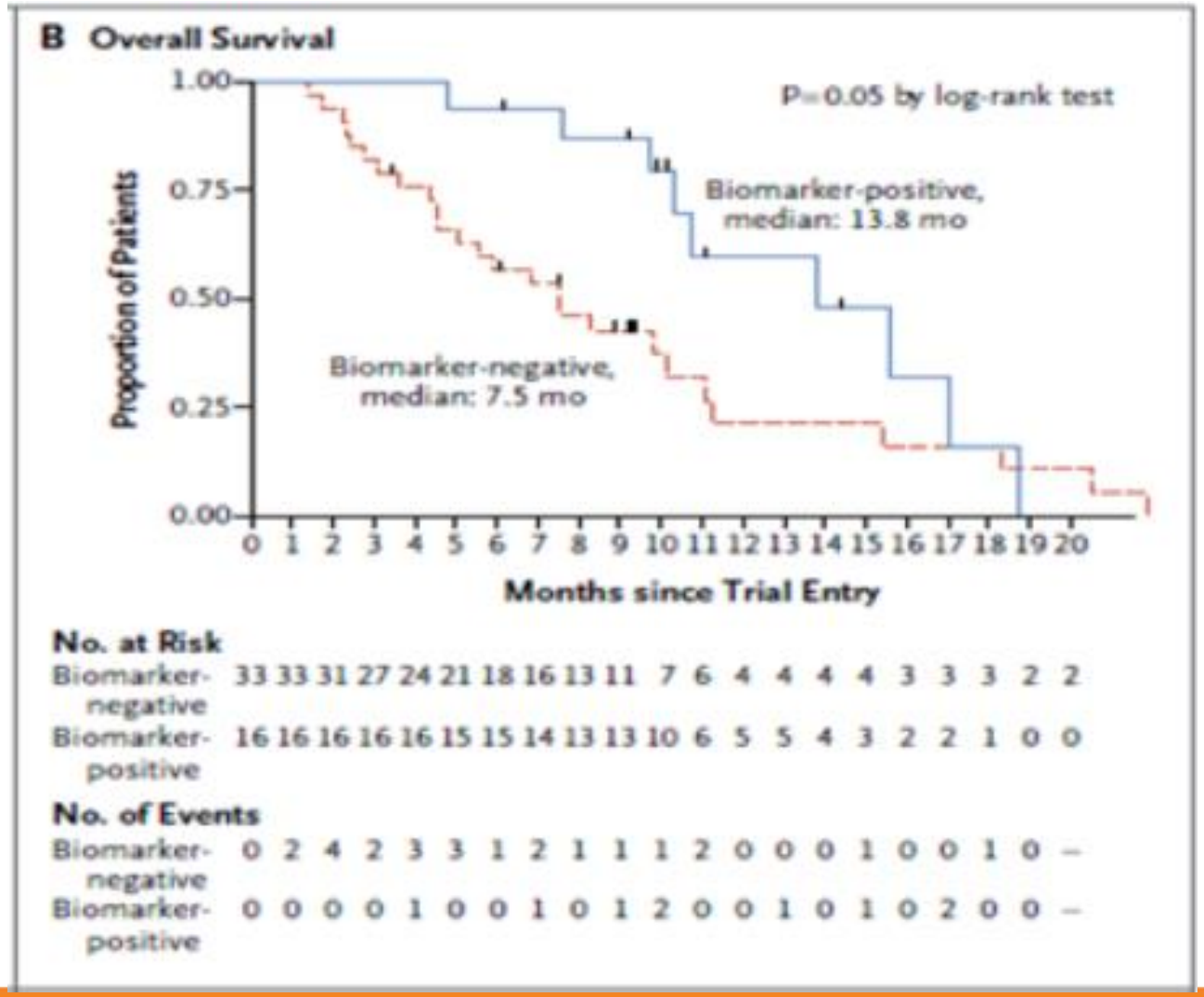
Figure 2. Distribution of Presumed Pathogenic Germline Mutations.

Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

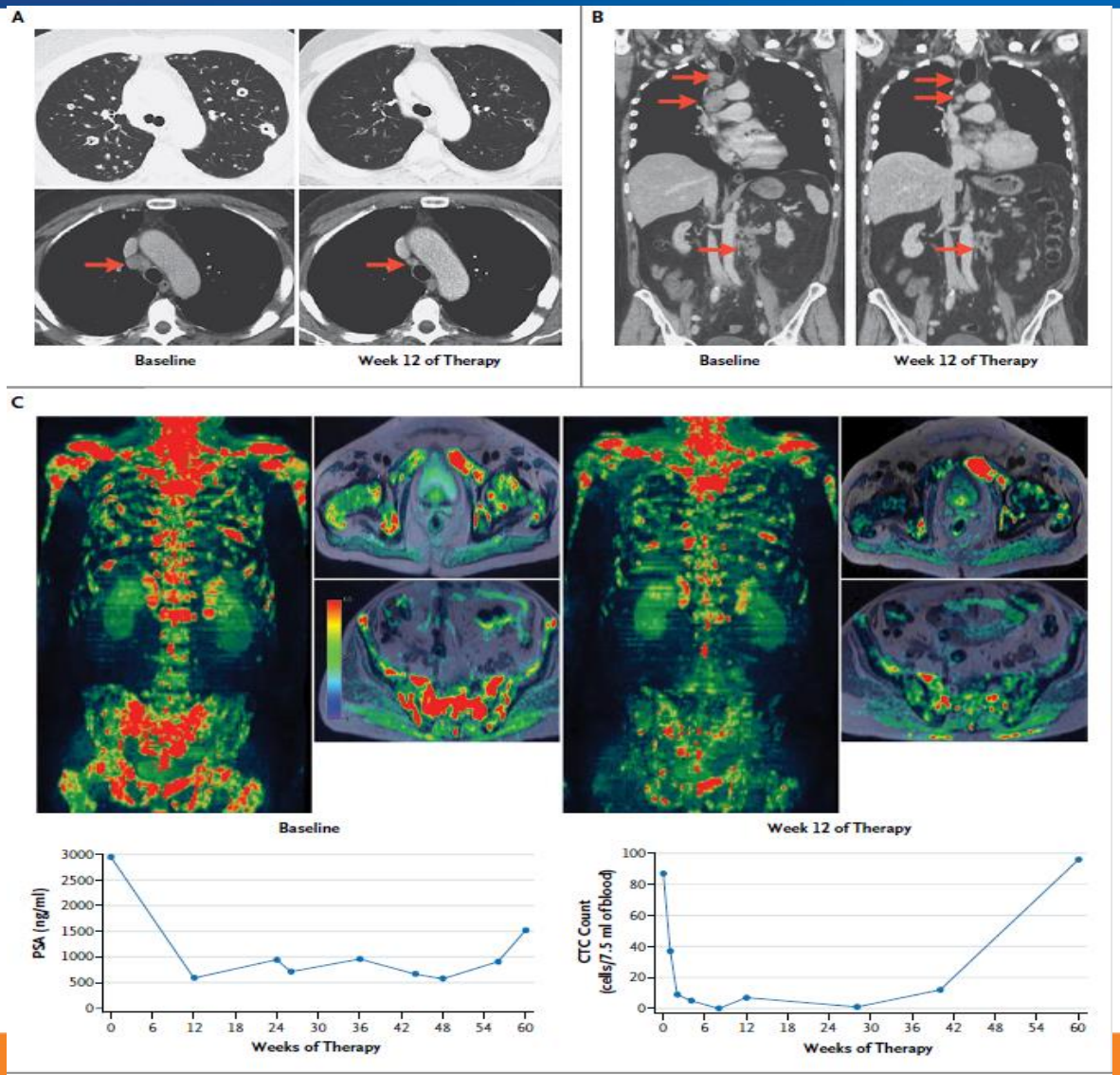


1. Many commonly utilized cancer chemotherapy regimens target tumor cells via fatal DNA lesions
2. Key DNA repair pathways (such as PARP) are upregulated in tumor cells - may lead to resistance
3. Inhibiting PARP may potentiate chemotherapy or be used as monotherapy in conditions with pre-existing DNA repair defects (such as BRCA negative)

OVERALL SURVIVAL FOR OLAPARIB

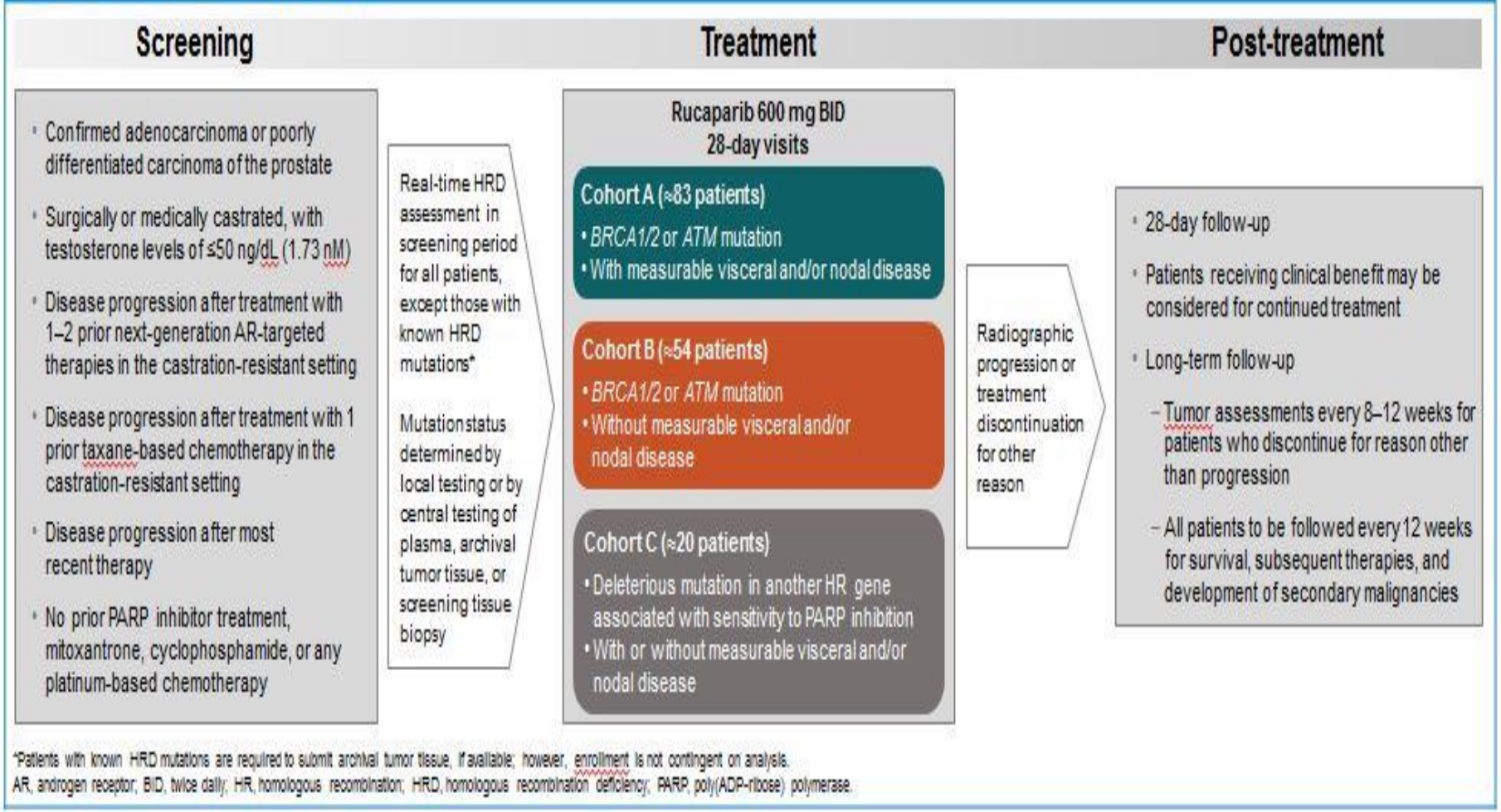


Radiologic Evidence of Tumor Responses to Olaparib



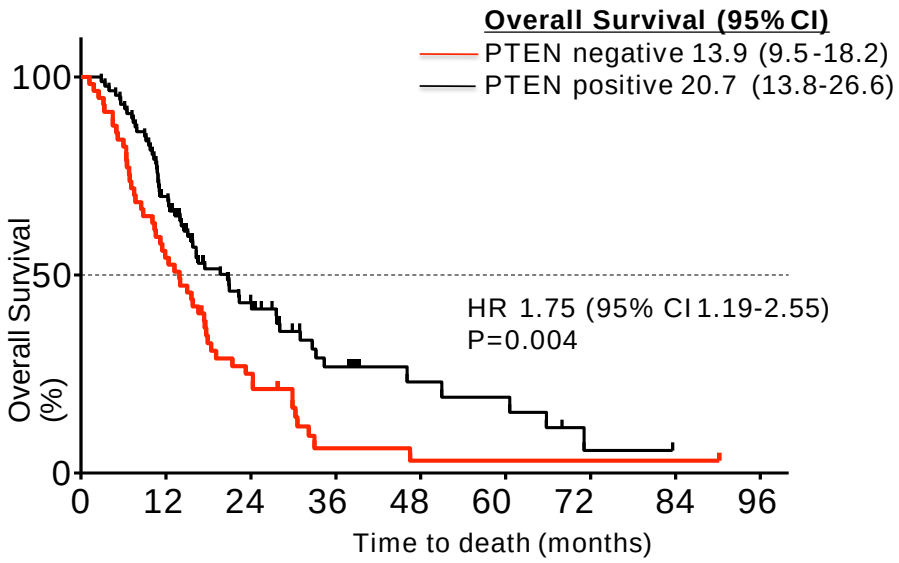
TRITON 2: A Multicenter Phase 2 Study of the PARP Inhibitor Rucaparib in Patients with Metastatic CRPC Associated with Homologous Recombination Deficiency

Figure 1. TRITON2 Study Design



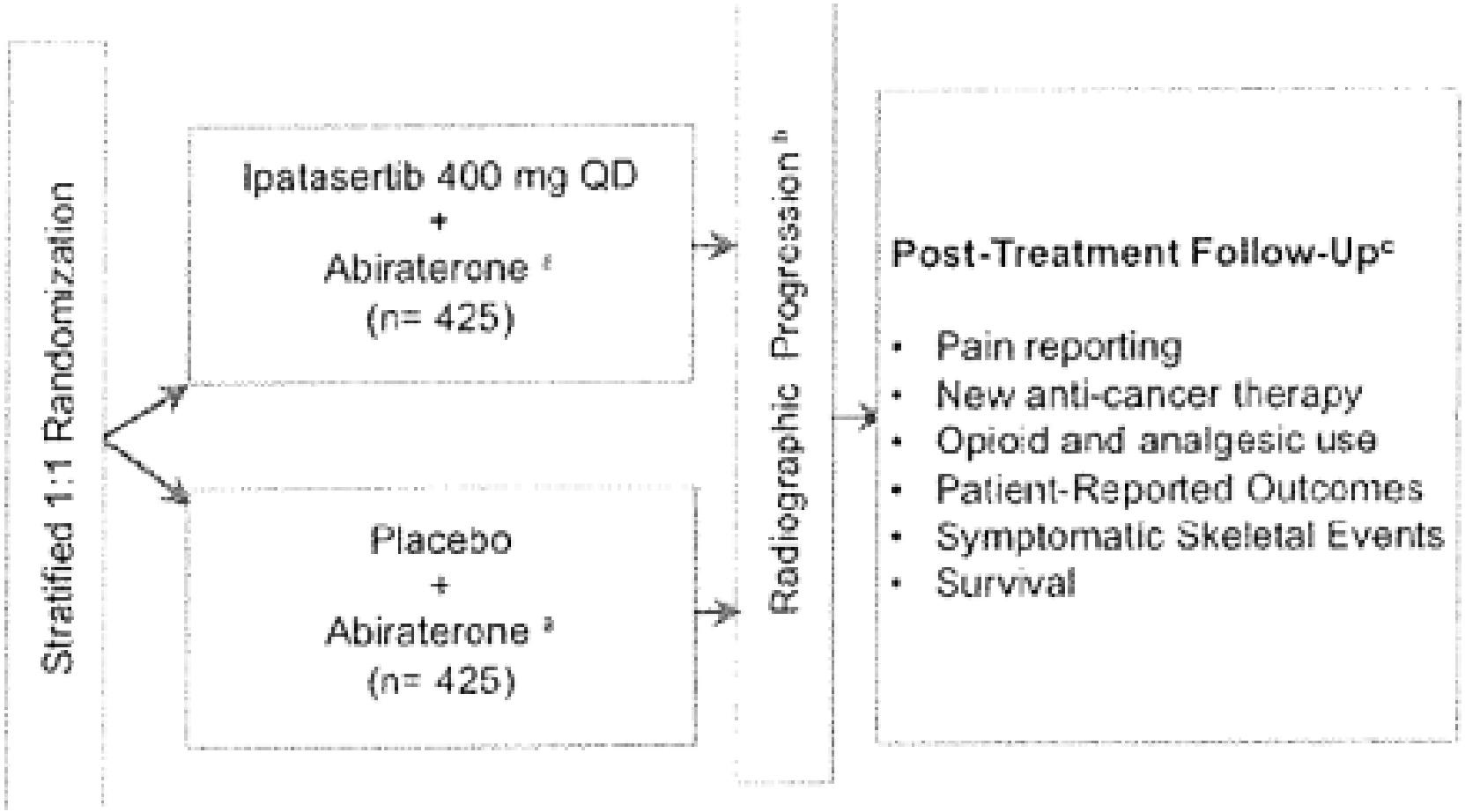
*Patients with known HRD mutations are required to submit archival tumor tissue, if available; however, enrollment is not contingent on analysis.
AR, androgen receptor; BID, twice daily; HR, homologous recombination; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

PTEN Loss and Prognosis in mCRPC



- In abiraterone-treated patients with mCRPC, PTEN loss by IHC was associated with a shorter mOS[1]
- Newly diagnosed, or surgically resected patients with PTEN loss or low expression demonstrated an increased risk for recurrence and death[1-6]
- Paired intra-patient tumor samples from either archival hormone-sensitive prostate tissues or castration-resistant fresh biopsies demonstrated a high concordance in PTEN status by IHC (86%)[1]

Clinical Trial of Abiraterone + Ipatasetib vs Aberaterone in mCRPC Patients

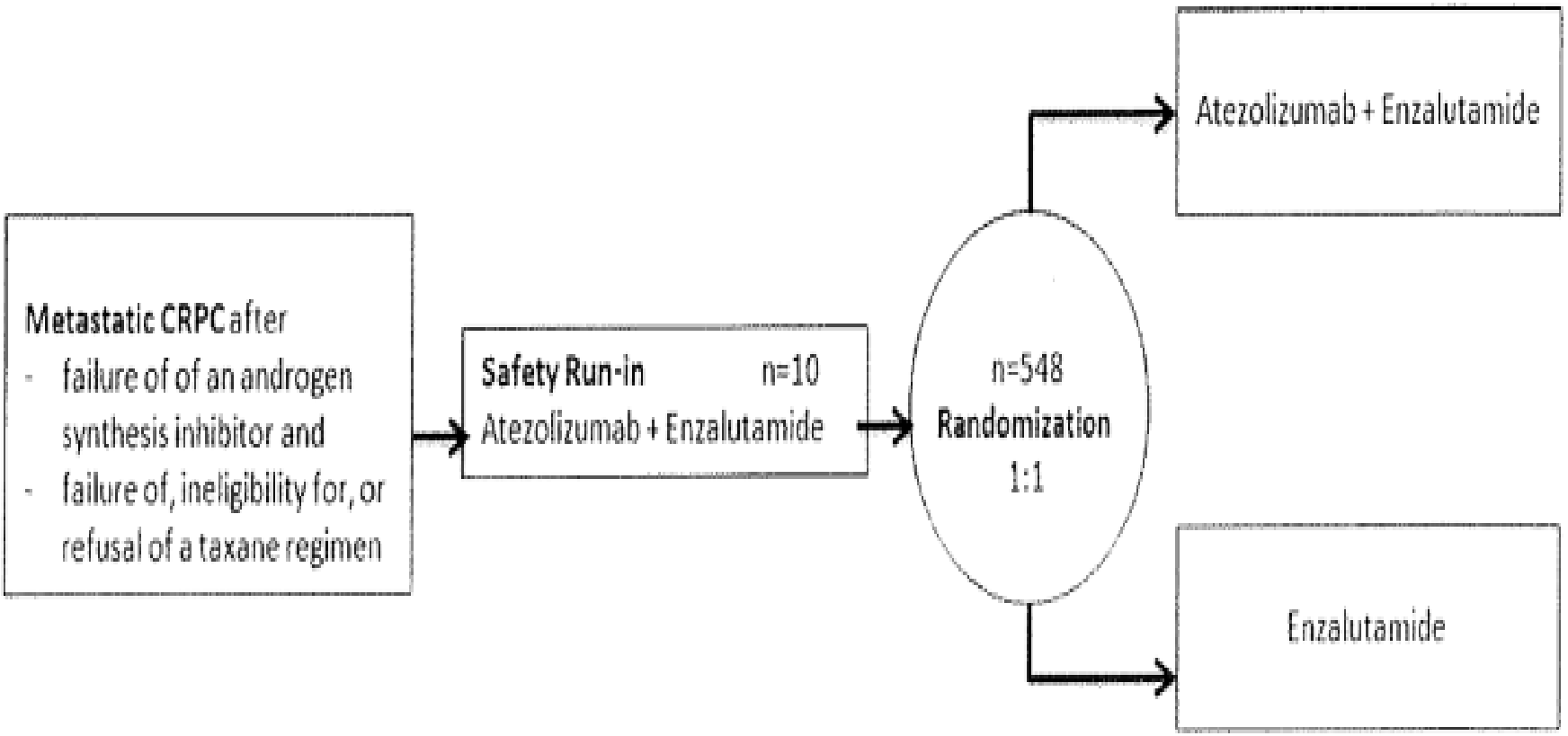


Revisiting anti-PD-1 Activity in Metastatic Castration- Resistant Prostate Cancer

- Prostate Cancer has a low mutation rate and limited infiltrating CD8 T-cells compared with melanoma and NSCLC where PD-1/PD-L blockade is effective
- Phase 1 trials in patient's with advanced prostate cancer have failed to show any objective responses to anti-PD-1 therapy
- A recent Phase 2 study showed unexpected clinical activity when Pembrolizumab (an anti-PD-1 antibody was administered to patients who had progressed on Enzalutamide
- Three of the first 10 patients treated had rapid PSA reductions to <0.2 ng/ml) and 2 patients with measureable disease at study entry had partial responses
- Biopsies obtained from these patients showed presence of CD8 tumor infiltration and PDl-1 expression

Graff JN et al: Oncotarget,Vol 7 (33) 2016

Clinical Trial of Enzalutamide + Atezolizumab vs Enzalutanide in mCRPC



Conclusions

- New insights into the adaptive changes that occur in the transition from hormone sensitive to CRPC has led to the development of new and more effective therapies
- The optimal sequence of agents has yet to be determined
- ARV7 is a promising biomarker for sensitivities to enzalutamide and abiraterone
- Docetaxel chemotherapy for hormone sensitive patients should be offered to high disease volume patients
- Immune therapy should be given early in asymptomatic non visceral mCRPC patients
- PARP inhibition is a promising therapeutic target in patents with BRCA mutations

PREVAIL Phase III Trial of Enzalutamide in Asymptomatic or Mildly Symptomatic mCRPC Pre Chemotherapy Preliminary Results

- Overall Survival 30% reduction in the risk of death (Hazard Ratio=0.70; 95% confidence interval,0.59-0.83)
- Progression Free Survival: 81% reduction in risk of radiographic progression or death compared with placebo (Hazard Ratio=0.19; 95% confidence interval, 0.15-0.23).

Current Management Options for Men With mCRPC

- Maintenance of castrate levels of testosterone (GnRH agonist/antagonists)
- Antiandrogens
  - Nilutamide, bicalutamide, flutamide, enzalutamide
- Immunotherapy
  - Sipuleucel-T
- Androgen synthesis inhibitors
  - Ketoconazole, abiraterone acetate
- Estrogens
- Chemotherapy
  - Docetaxel, cabazitaxel
  - Mitoxantrone
- Radiopharmaceuticals
  - Radium 223
- Supportive care
  - Bone health: exercise, bisphosphonates, denosumab
  - Vitamin D and calcium

GnRH=gonadotropin-releasing hormone.

NCCN. Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology. V4.2013

Prognostic Factors in CRPC

Pre-treatment Prognostic Factors

- Performance status
- Gleason sum
- Visceral disease, number of sites of disease
- Anemia
- Alkaline phosphatase, urine NTx levels
- Pain
- PSA and PSA kinetics
- CTC count
- LDH, CRP levels
- Albumin
- Type of progression (bone, measurable disease, PSA only)
- Age
- VEGF, IL-6, chromogranin levels

Post-treatment Prognostic Factors

- PSA declines
- Pain improvement
- Quality of life improvement
- Change in CTC count (>5 to <5)
- PSA and PFS
- Immune response parameters

CTC=circulating tumor cell; LDH=lactate dehydrogenase; CRP=C-reactive protein; VEGF=vascular endothelial growth factor; PFS=progression-free survival.

Smaletz O et al. *J Clin Oncol*. 2002;20:3972-3982; Halabi S et al. *J Clin Oncol*. 2003;21:1232-1237; Armstrong AJ et al. *Clin Cancer Res*. 2007;12:6396-6403.

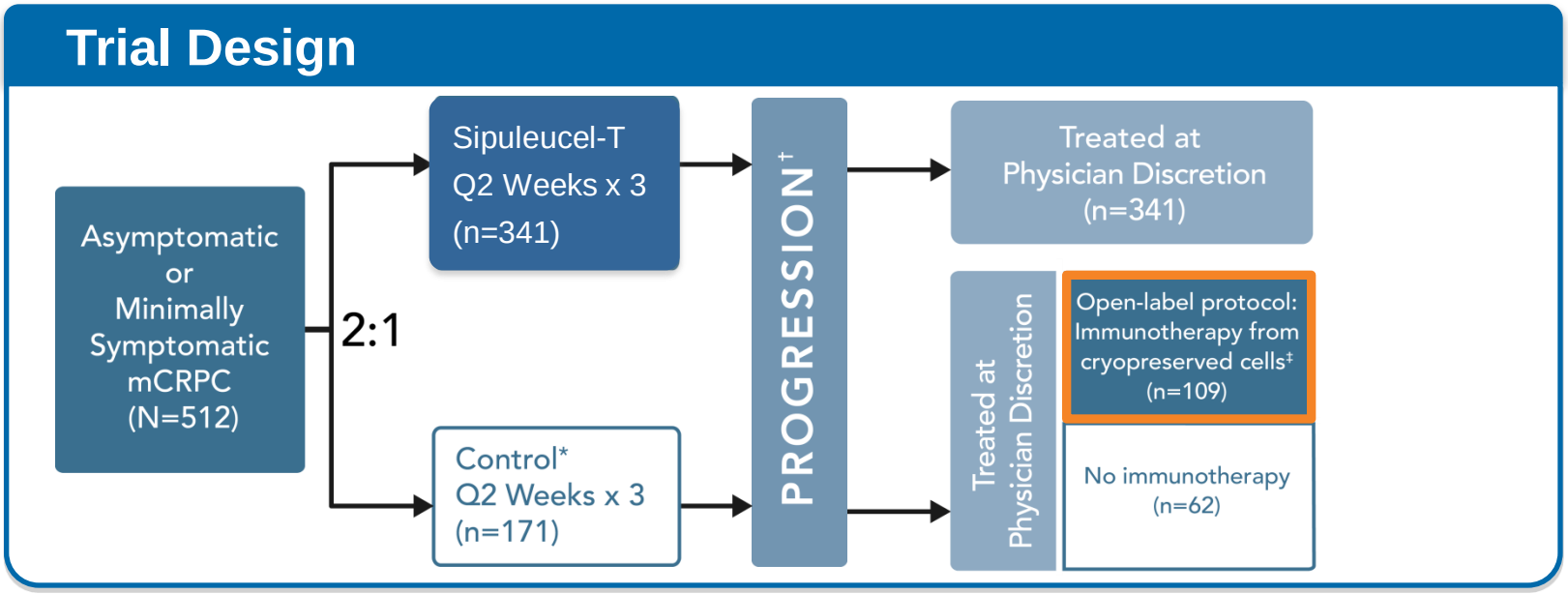
Role of Prognostic Models and Factors in the Clinic

- Nomograms may help guide discussions about expectations with patients and the need for more or less aggressive therapies
- Can identify men with asymptomatic or minimally symptomatic mCRPC who may benefit from immunotherapy
- May help identify men based on certain prognostic categories (pain, hepatic metastases, rapid disease progression) who are more appropriate for chemotherapy

Smaletz O et al. *J Clin Oncol*. 2002;20:3972-3982; Halabi S et al. *J Clin Oncol*. 2003;21:1232-1237; Bitting RL, Armstrong AJ. ASCO 2012.

IMPACT Trial Design

- Phase 3, randomized, double-blind, controlled study
- Primary endpoint—overall survival



64% of patients in the control group, following progression, crossed over to a nonrandomized, open-label protocol

- They received investigational autologous immunotherapy made from cryopreserved cells
- Treatment in the open-label protocol was at the physician's discretion

*Control was nonactivated, autologous, peripheral blood mononuclear cells. †Progression=radiographic evidence of disease progression.
‡Autologous, peripheral blood mononuclear cells that were cryopreserved at the time of control generation and subsequently activated.

Kantoff PW et al. *N Engl J Med*. 2010;363:411-422.

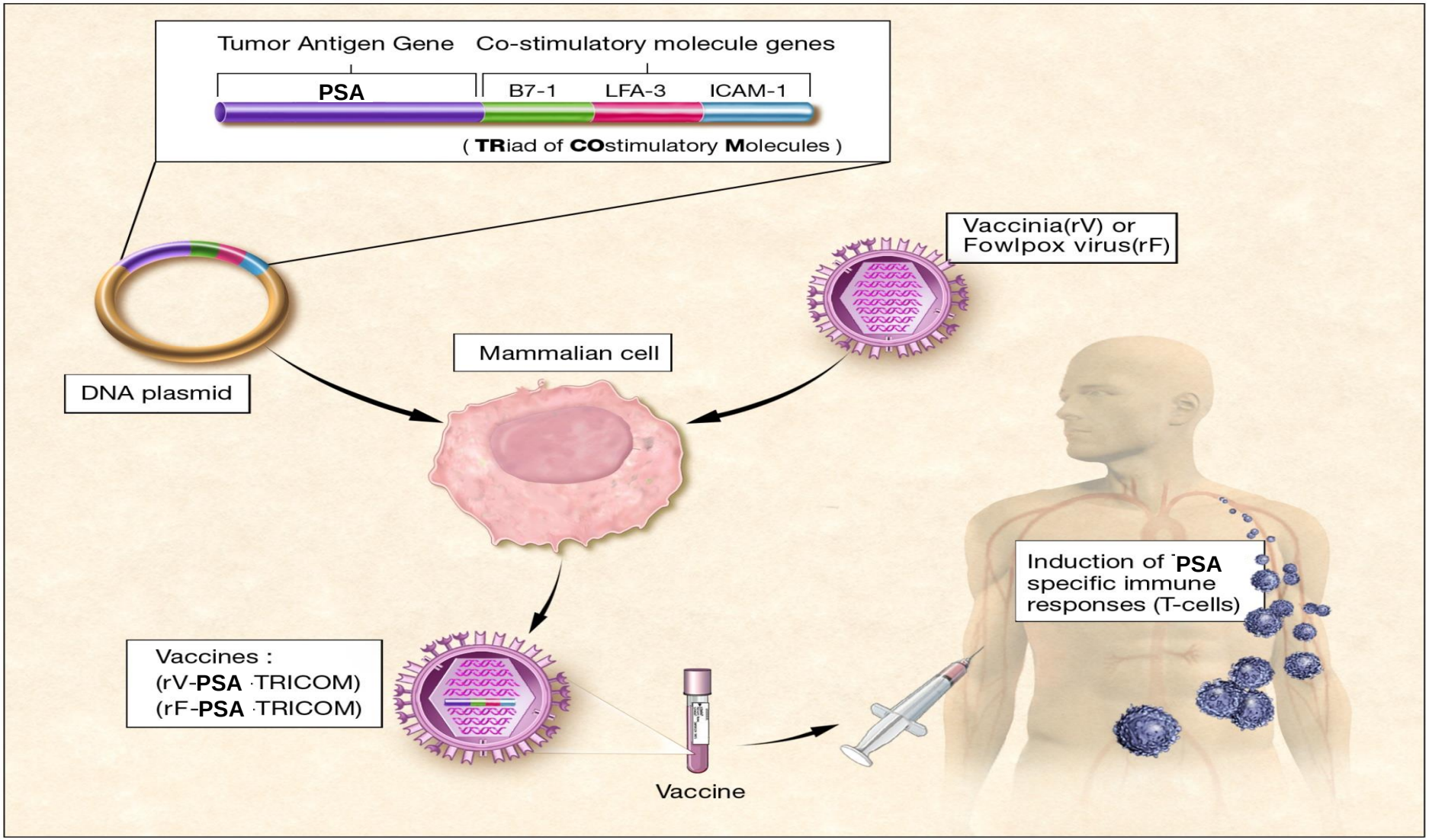
IMPACT Trial: Baseline Characteristics

Baseline Characteristics

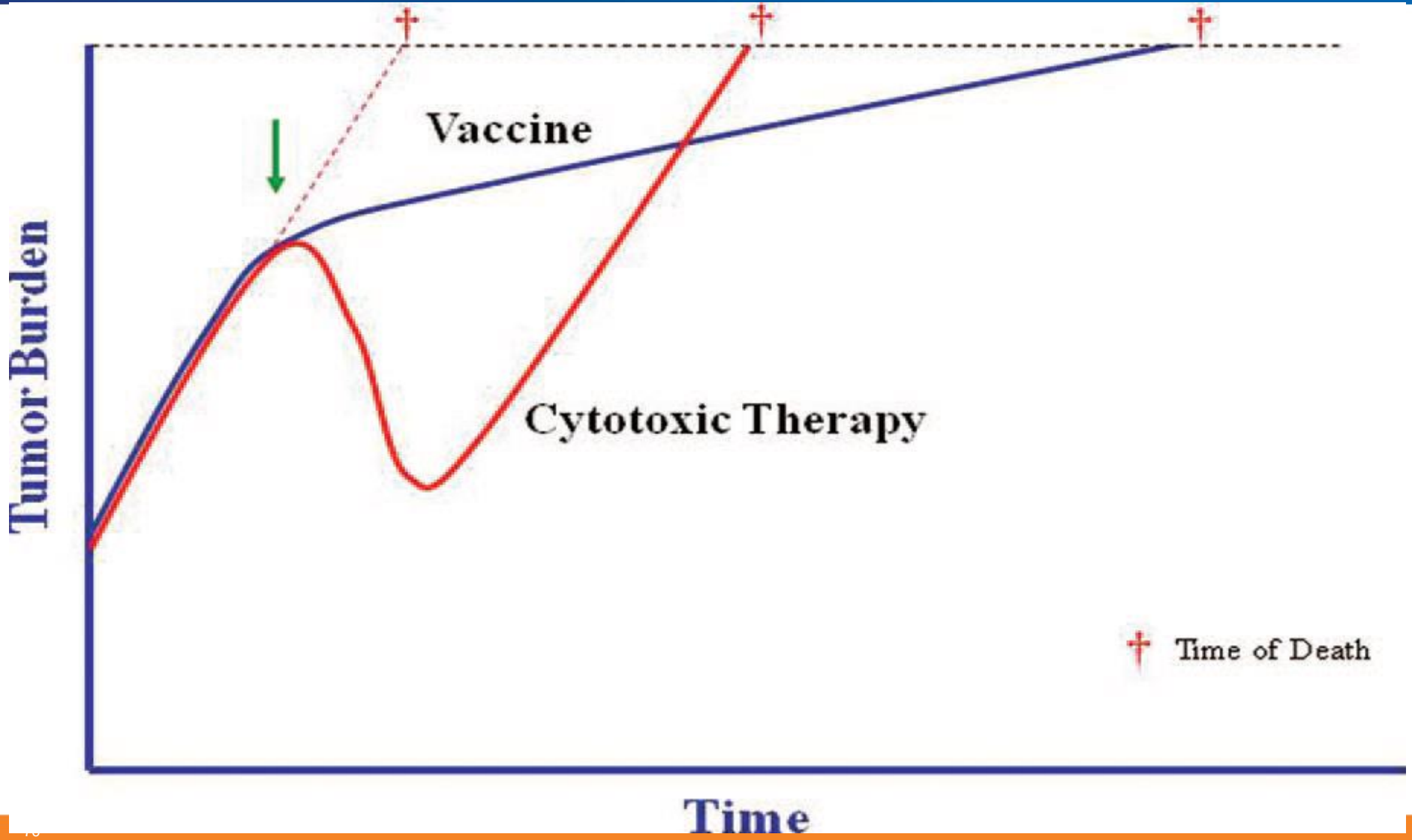
	Sipuleucel-T (n=341)	Control (n=171)
Age, median, years (range)	72 (49-91)	70 (40-89)
Race, white (%)	89.4	91.2
ECOG status 0 (%)	82.1	81.3
Gleason sum ≤7 (%)	75.4	75.4
PSA (ng/mL)	51.7	47.2
Disease localization		
Bone only (%)	50.7	43.3
Soft tissue only (%)	7.0	8.2
Bone and soft tissue (%)	41.9	48.5
>10 bone metastases (%)	42.8	42.7
Bisphosphonate use (%)	48.1	48.0
Prior docetaxel (%)	15.5	12.3

ECOG=Eastern Cooperative Oncology Group.

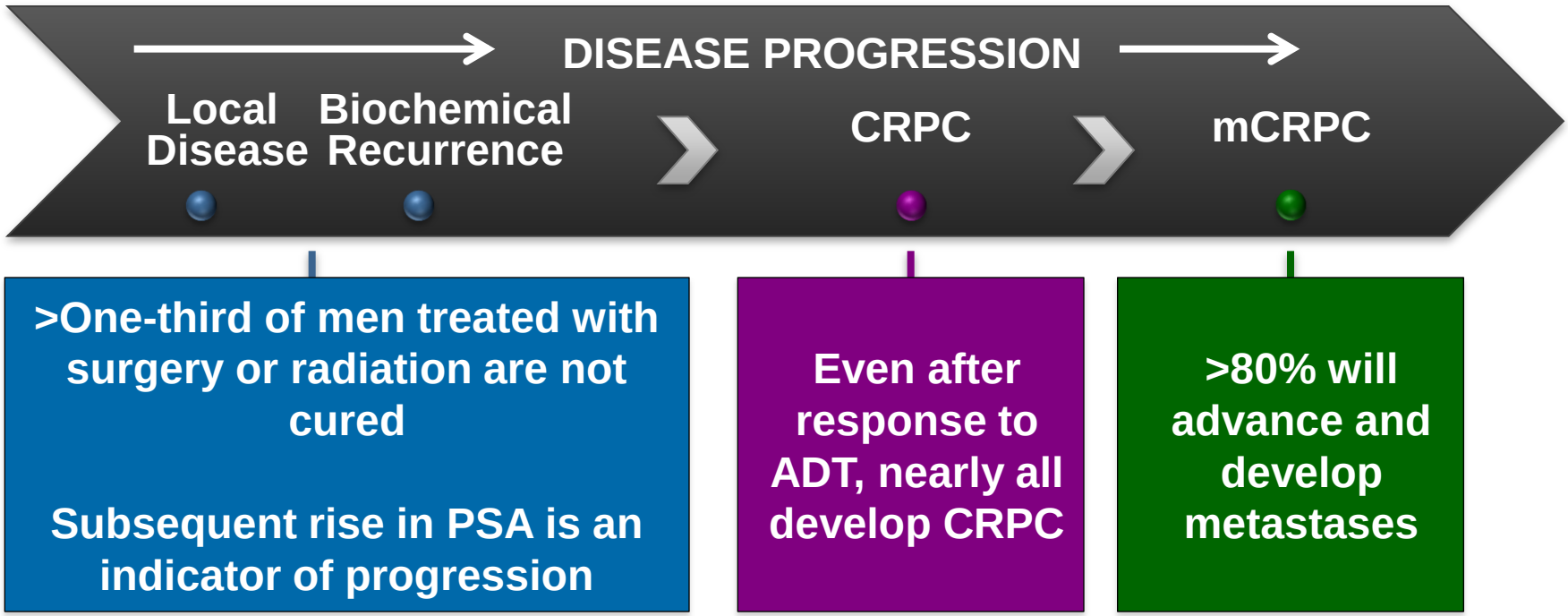
Prostvac Vaccine



Immunotherapy Work Differently to Change The Course of the Disease



Following Treatment with Surgery or RT, Prostate Cancer Often Progresses



CRPC=castration-resistant prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; PSA=prostate-specific antigen; ADT=androgen deprivation therapy.

American Cancer Society. *Cancer Facts & Figures.* 2013. Atlanta:American Cancer Society; 2013; D'Amico A et al. *N Engl J Med*. 2004;351;125-136; D'Amico A et al. *JAMA* 2005;294;440-477; Penson DF. *Clin Adv Hematol Oncol*. 2011; Kirby M et al. *Int J Clin Pract*. 2011;65:1180-1192.