Current and Evolving Targeted Therapies for the Treatment of Metastatic Prostate Cancer

Alan J. Koletsky, MD

Eugene and Christine Lynn Cancer Institute
Clinical Associate Professor
Charles E Schmidt College of Medicine
Boca Raton, FL

Prostate Cancer

Overview of Targeted Therapies

Treatments targeting the Androgen Receptor

Immunotherapeutic approaches to treatment
- -- Sipuleucel-T
- -- Immune checkpoint therapy

Treatment based on alterations in DNA repair
- -- Olaparib
- -- Rucaparib
- -- Combination Therapy

PSMA-targeted therapies

Major Categories of Therapies for ADT-Resistant Prostate Cancer in 2020

Hormonal Agents	Abiraterone Enzalutamide, Apalutamide, Darolutamide
Immunotherapy	Sipuleucel T Pembrolzumab Future: PSMA-directed antibodies; CART cells
Chemotherapy	Docetaxel , Cabazitaxel, Carboplatin Mitoxantrone
Radiopharmaceutical	Radium - 223

How do we sequence these agents?

- Clinical Characteristics
  - Symptomatic vs Asymptomatic
  - Visceral vs Non Visceral
  - Pre vs Post Docetaxel
  - HSPC vs CRPC
- Biological Markers
  - Androgen Receptor
  - DNA Repair
  - MSI

Chemotherapy – Historical Use in Metastatic Castration-Resistant Patients

Usually Reserved for CRPC Patients who were

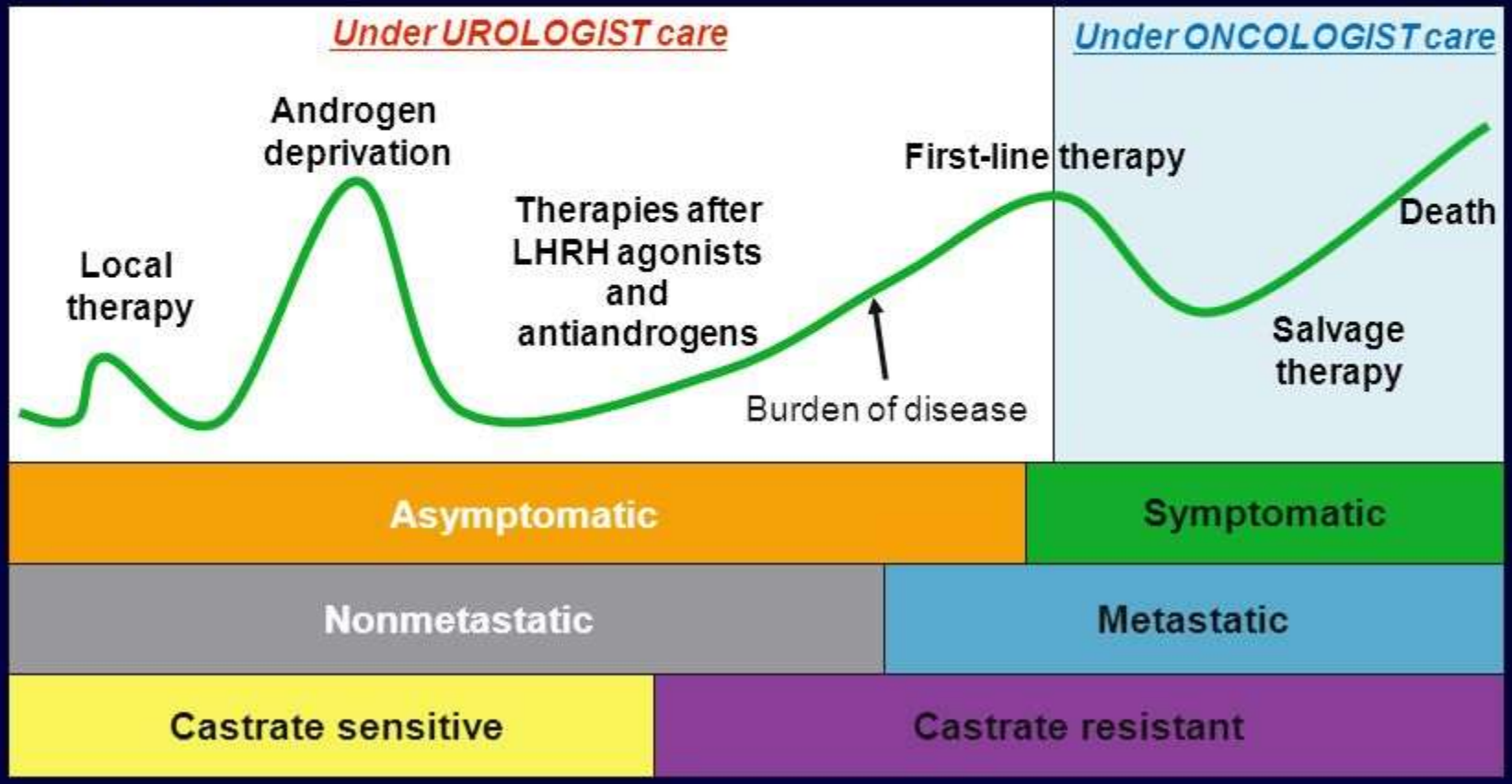
Symptomatic

Rapidly Progressing

Had Visceral Disease

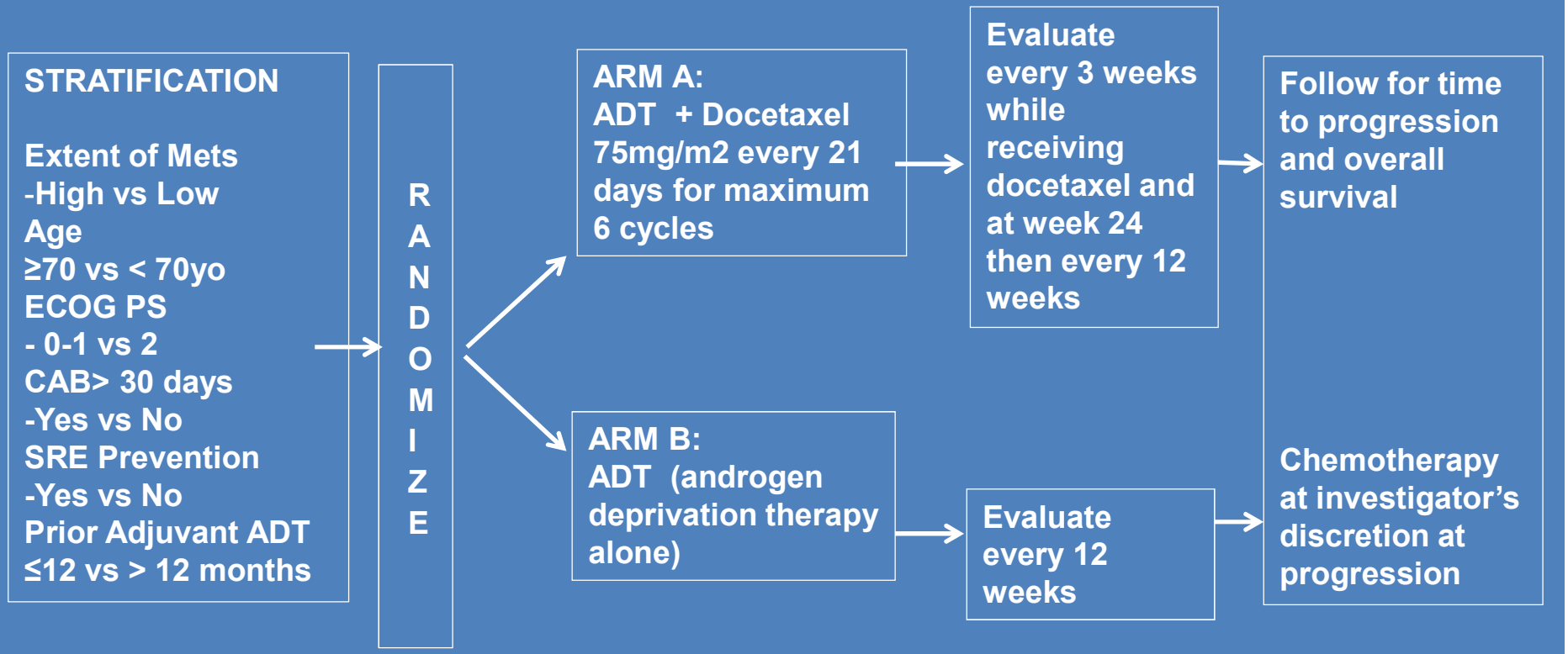
Natural History of Prostate Cancer

- Typical patient presentation as they move through different stages



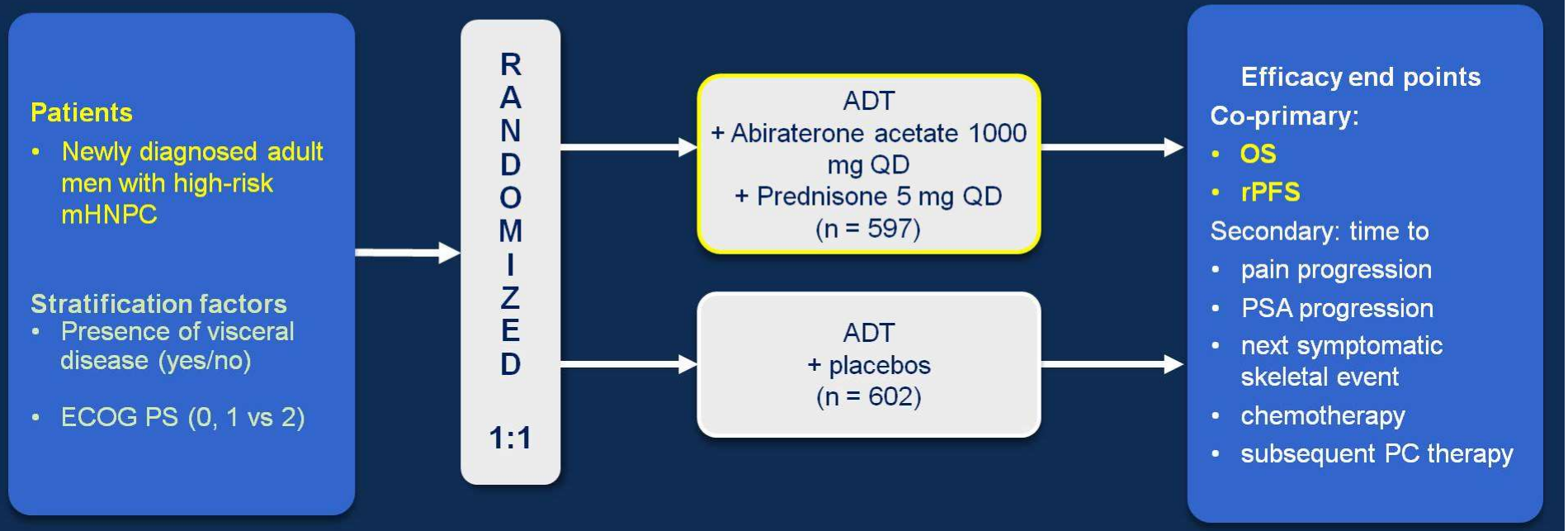
Higano C, et al. In: Figg WD, et al. Drug management of prostate cancer; 2010.

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



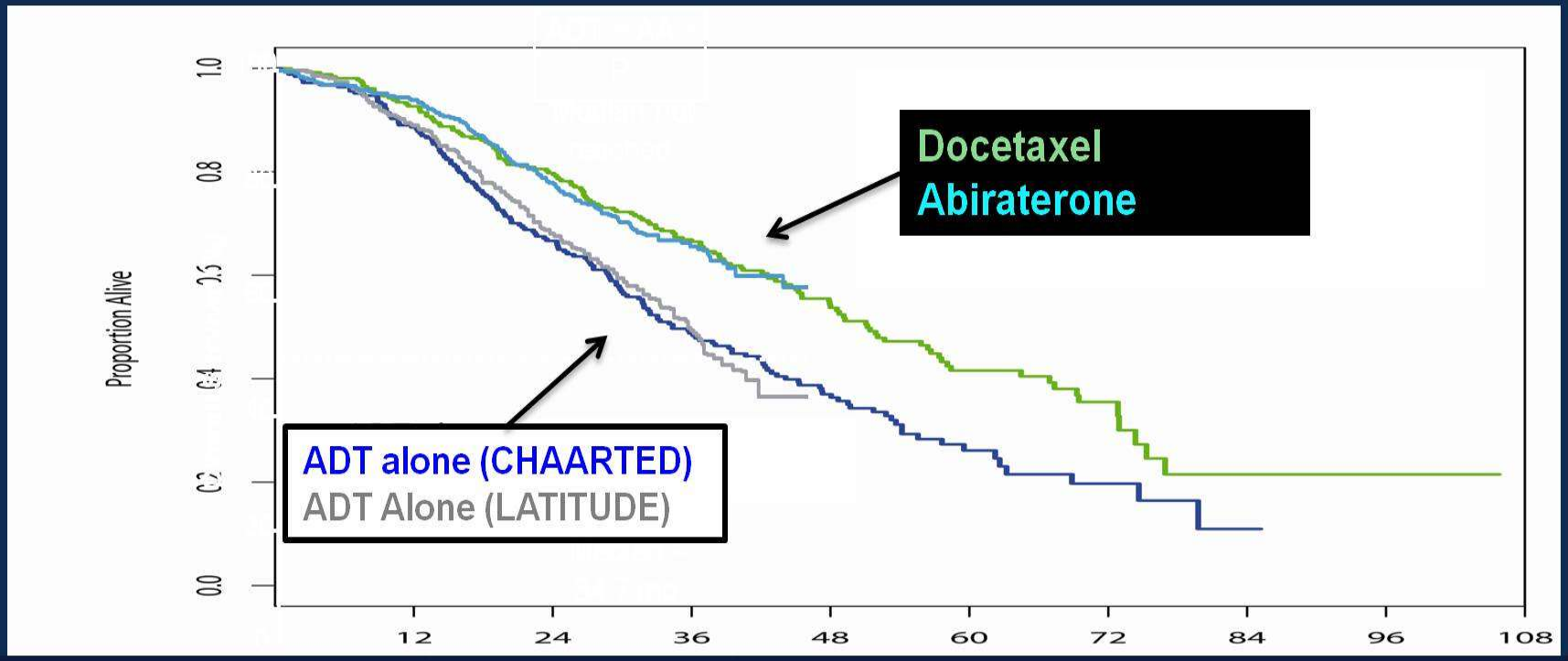
- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Overall study design of LATITUDE



- **Conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada**
- **Designed and fully enrolled prior to publication of CHAARTED/STAMPEDE results**

Docetaxel vs. Abiraterone



Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

Docetaxel vs. Abiraterone

Comparing Overall Survival Across Studies

	Median OS			3 yr OS rate	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
STAMPEDE	0.63	not reached (0.52 – 0.76)			
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%*	~65%*

Chemohormonal Therapy for mHSPC

- **CHAARTED Study**
  - **High volume disease: ≥4 bony metastases, at least one outside of axial skeleton and/or visceral metastases**
  - **17 mo overall survival benefit *only in high volume disease*** (pre-specified analysis)
  - **No overall survival benefit in low volume disease**

- **STAMPEDE Study**
  - **Did not stratify by low vs high volume disease**

- **Conclusions**

  Standard of care for high volume disease: ADT + docetaxel

  -- Standard of care for low volume disease:

  -- ADT alone (CHAARTED) or

  -- ADT + docetaxel (STAMPEDE)

Phase 3 TITAN
ADT + apalutamide vs ADT and placebo for mHSPC

"All-comer" patient population

Key Eligibility Criteria
Castration sensitive
Distant metastatic disease by ≥ 1 lesion on bone scan
ECOG PS 0 or 1

On-Study Requirement
Continuous ADT

Permitted
Prior docetaxel
ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
Local treatment completed ≥ 1 yr prior

Stratifications
Gleason score at diagnosis (≤ 7 vs ≥ 8)
Region (NA and EU vs all other countries)
Prior docetaxel (yes vs no)

N = 1052

Dec 2015 – Jul 2017

1:1 RANDOMIZATION

- **Apalutamide 240 mg daily + ADT (n = 525)**
- **Placebo + ADT (n = 527)**

Dual primary end points
- **OS**
- **rPFS**

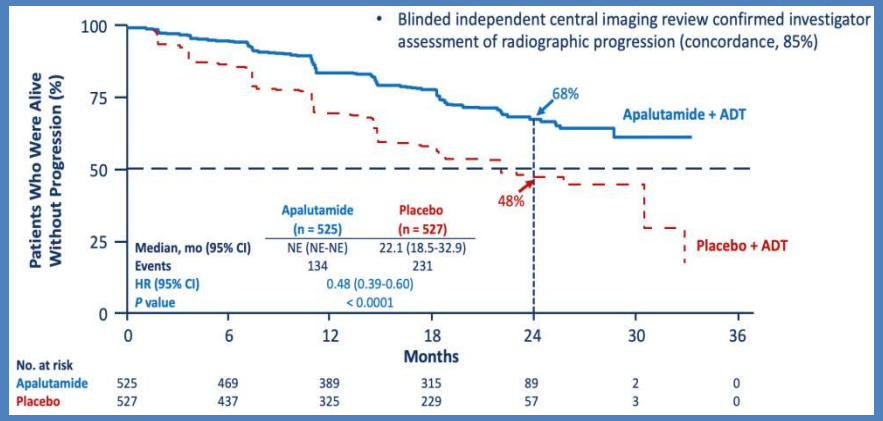
Secondary end points
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

Exploratory end points
- Time to PSA progression
- Second progression-free survival (PFS2)
- Time to symptomatic progression

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, North America; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

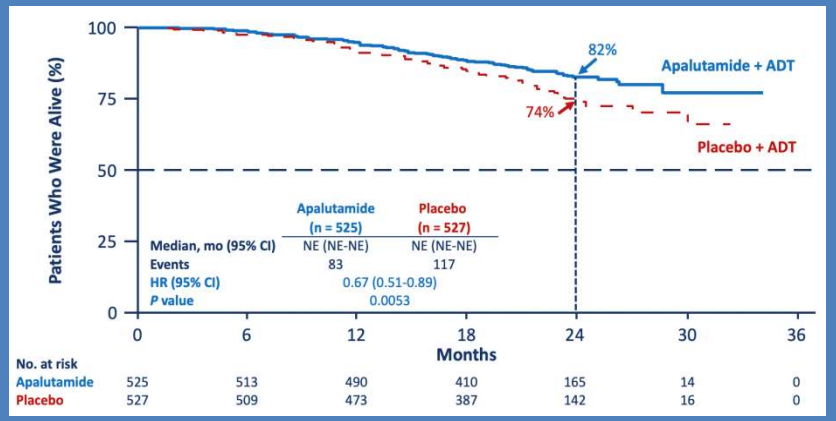
Phase 3 TITAN
ADT + Apalutamide vs ADT and Placebo for mHSPC

rPFS



- 20% difference in rPFS at 2 years
- Reduced risk of radiographic progression by 52%

OS

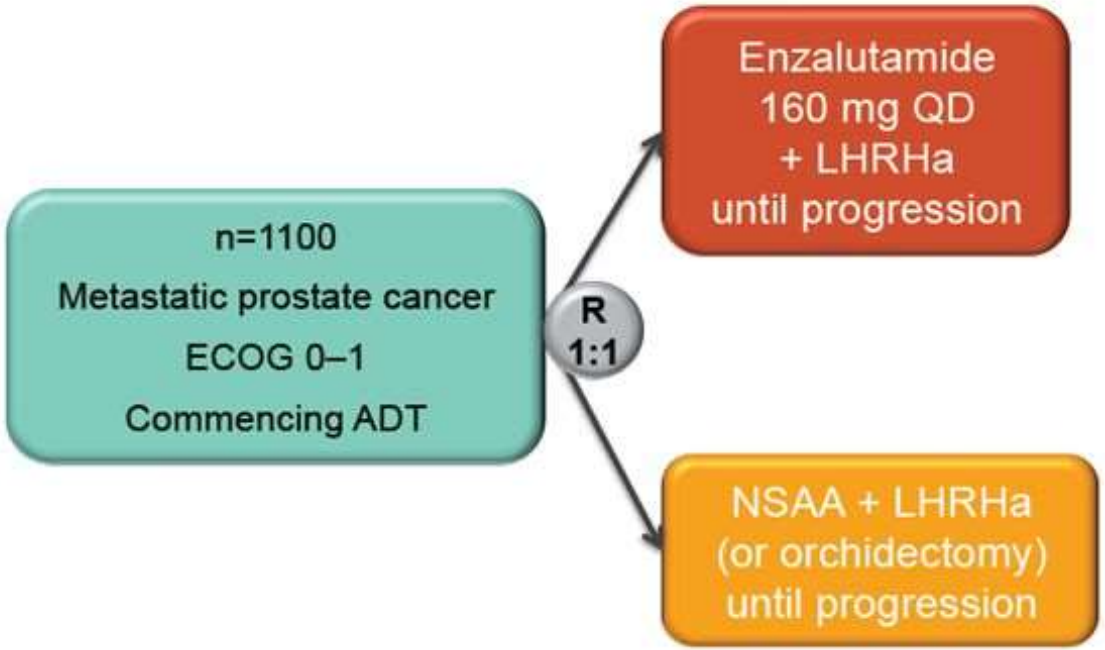


- 8% difference in OS at 2 years
- Reduced risk of death by 33%

More rash, fatigue, hypothyroidism, fracture with apalutamide

CS Higano, MD, FACP

ANZUP ENZAMET: ADT ± enzalutamide in metastatic prostate cancer commencing ADT (M1 ADPC)



Recruiting (subject to revision)
FPI March 2014

Planned evaluations

- Primary endpoint: OS
- Secondary endpoints:
  - PFS
  - TT PSA
  - QoL
  - Cost effectiveness

Stratification

- Volume of disease
- Antiresorptive therapy
- Comorbidities
- Study site

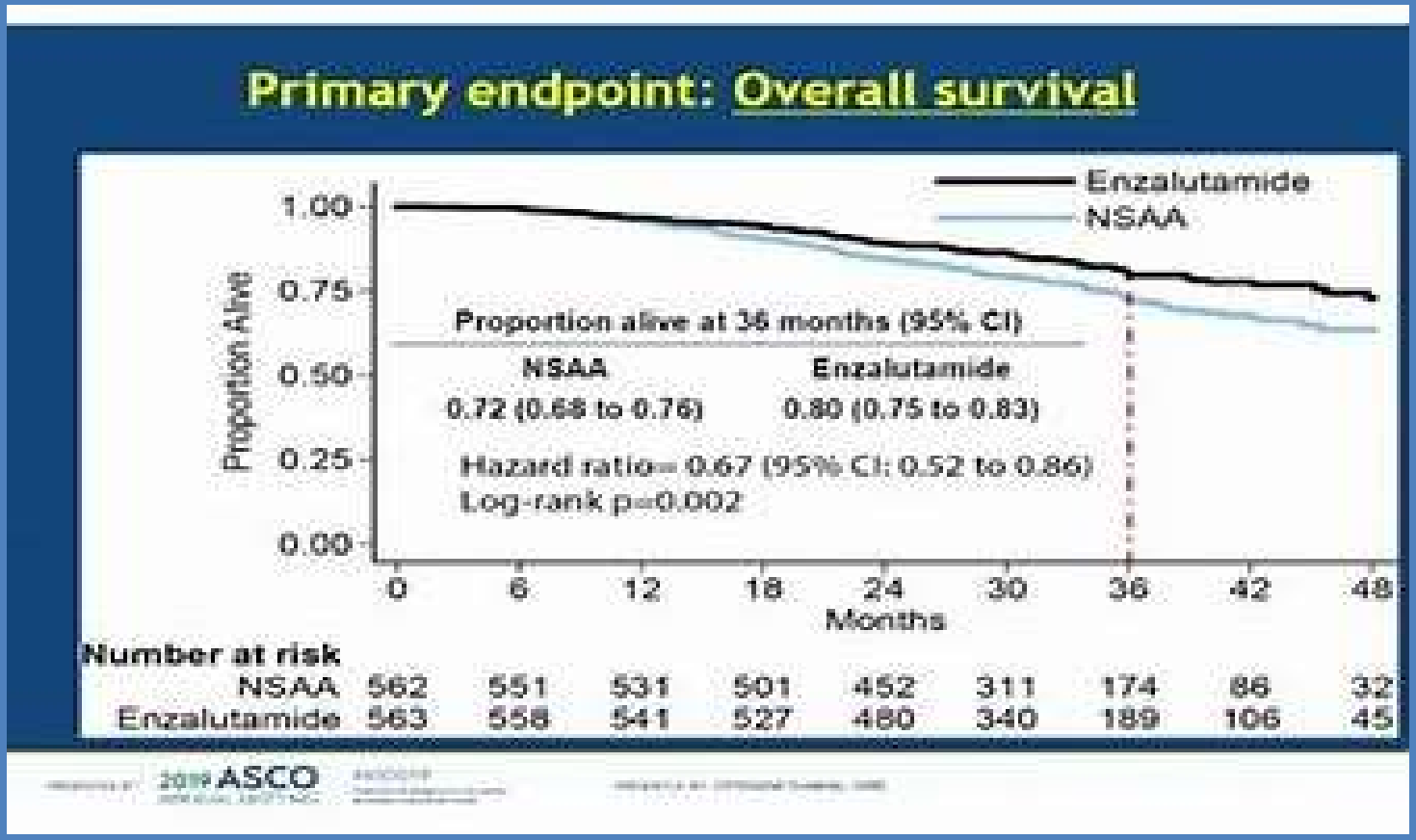
Statistical analysis

- 80% power
- 471 events
- 25% reduction in HR
- Assume 3-year survival 65%
- 2-sided type 1 error 0.05

ADPC=androgen-dependent prostate cancer; ADT=androgen-deprivation therapy; ANZUP=Australian and New Zealand Urogenital and Prostate Cancer Trials Group; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LHRHa=luteinising hormone-releasing hormone agonist; NSAA=non-steroidal anti-androgen; OS=overall survival; PFS=progression-free survival; PSA=prostate-specific antigen; QD-once daily; QoL=quality of life; TT=time to.

ACTRN12614000110684. Available at: https://www.anzctr.org.au/Trial/Registration/TrialReview. Last accessed: June 2014.

ENZAMET: ADT + /- enzalutamide in metastatic prostate cancer commencing ADT (M1 ADPC)



Current Treatment Options for Metastatic Hormone Sensitive Prostate Cancer (mHSPC)

Trial	Drug	Comparison
CHAARTED	docetaxel	ADT
STAMPEDE	abiraterone	ADT
LATITUDE	abiraterone	ADT
TITAN	apalutamide	ADT (+/- doce 11%)
ENZAMET (LBA)	Enzalutamide	ADT (+/- doce 45%)

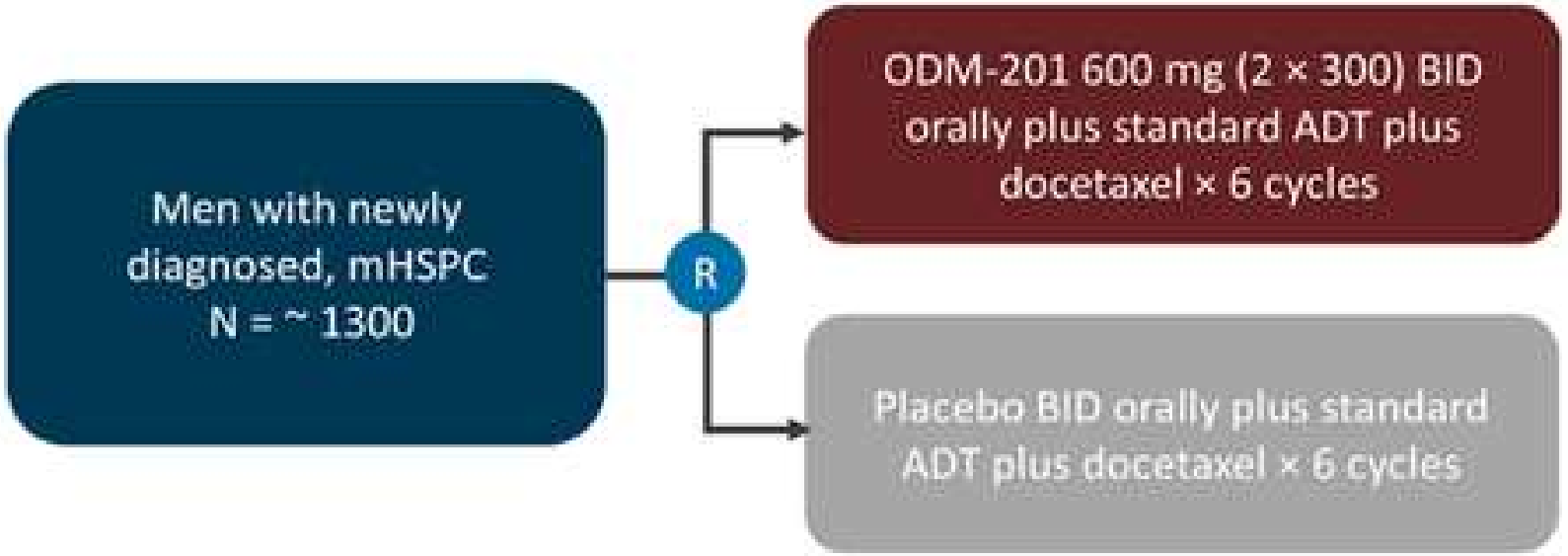
How will we choose between the up-front agents?

	DOCETAXEL	ABIRATERONE	ENZALUTAMIDE (APALUTAMIDE)
Length of Treatment	**Short term** approx 4.5 months	Long term approx 33 mo	Long term >36 months
Financial	possible time off work	Prescription co-pays; **generic**	Prescription co-pays
Select Toxicities	Peripheral neuropathy, hair loss	Liver enzymes, electrolytes, HTN	CNS (seizures/ cognitive), falls
Corticosteroids	YES	YES	**NO**
Subsets	High-volume*	Any	Any

*≥4 bone mets with 1 outside axial skeleton OR visceral mets

ARASENS: Randomized, Double-Blind, Phase 3 Trial of ODM-201* in mHSPC

- Study initiated: November 2016
- Primary endpoint: OS
- Approach: combining chemotherapy and AR-targeted therapy



*Darolutamide.
ClinicalTrials.gov. NCT02799602.

Definition of CRPC

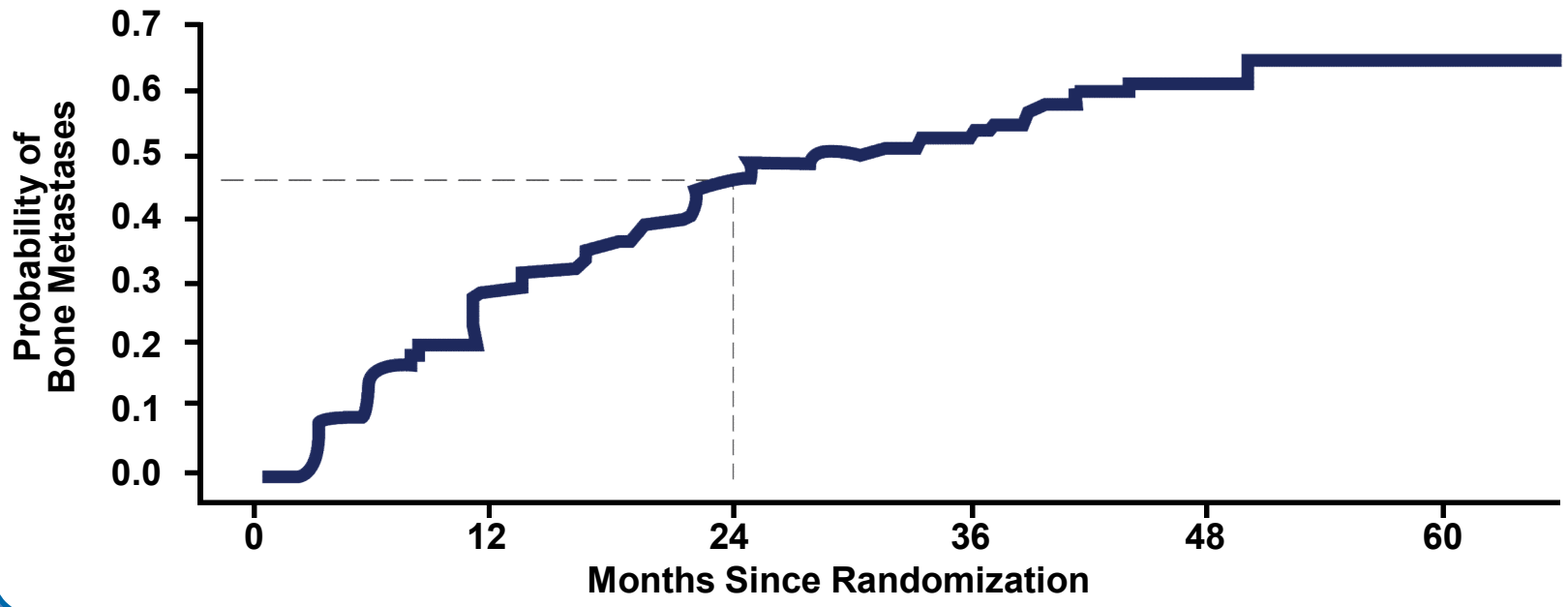
- Castrate level of serum testosterone
  - Currently, T < 50 ng/dL is most accepted
- Increasing PSAs or progressive disease on imaging
- Historical (but not accurate) terminology
  - Hormone refractory
  - Androgen independent

Scher HI, et al. J Clin Oncol. 2008;26:1148-1159.

Progression to mCRPC is Rapid

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

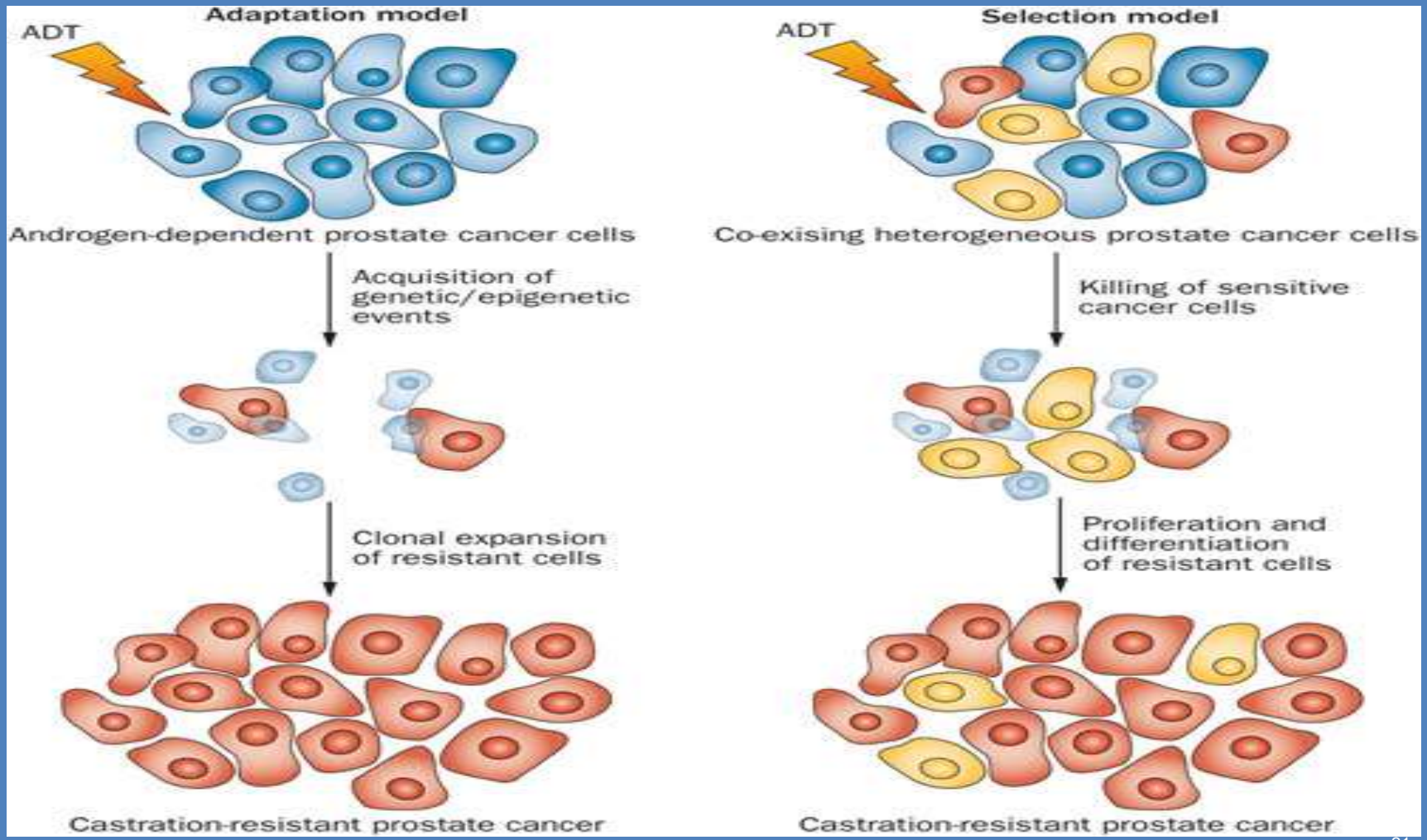
Time to Onset of Metastases in Men With CRPC



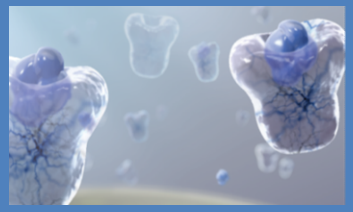
Data are from the placebo arm (n=331) of a randomized, controlled study to evaluate the effects of atrasentan on time to disease progression in men who had progressive CRPC and no radiographic evidence of bone metastases.

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

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

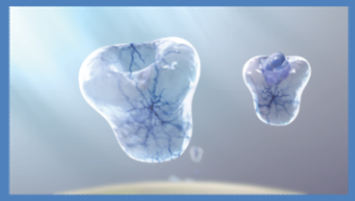


Continued AR Signaling in CRPC is Driven Through Aberrant Mechanisms



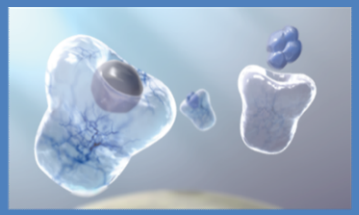
AR Overexpression

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



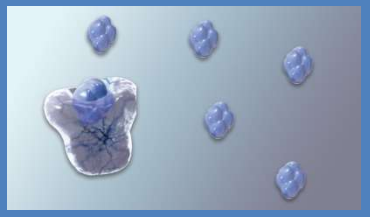
Androgen-Independent Activation

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



AR Promiscuity

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



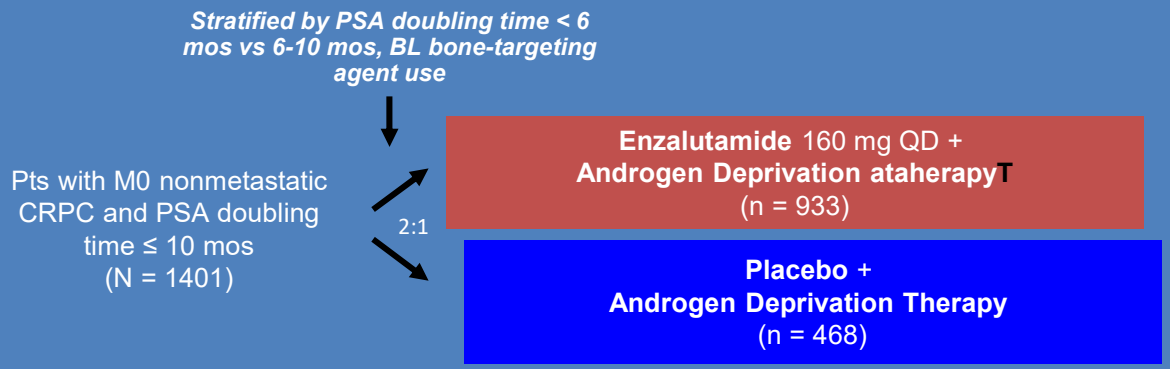
Intratumoral Production of Androgen

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

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

076-1263-PM 12/15

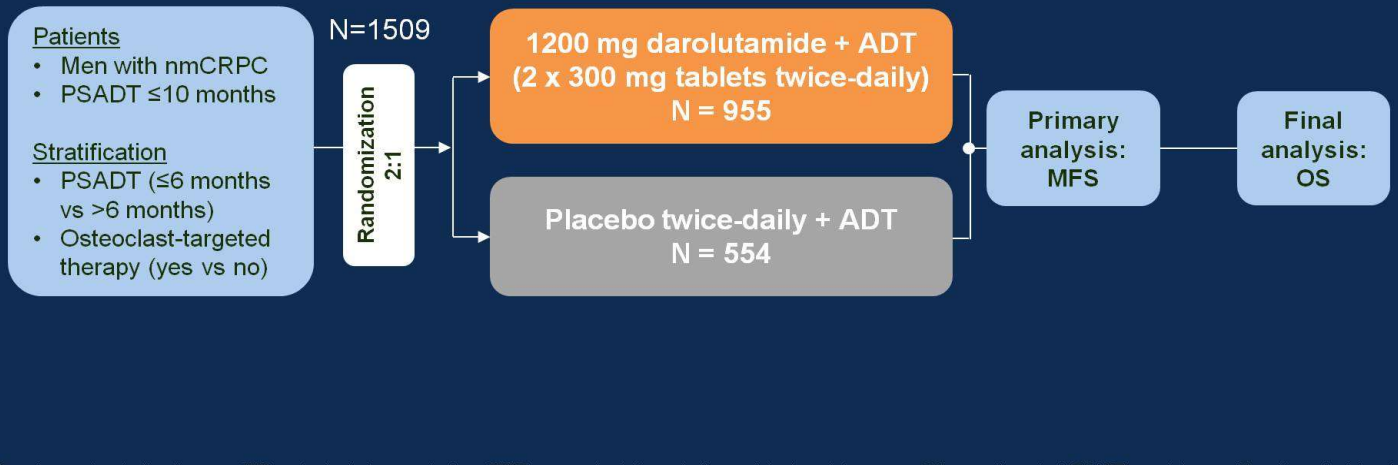
Enzalutamide vs Placebo in Nonmetastatic CRPC (PROSPER): Phase III Study Design



- **Primary endpoint: metastasis-free survival**
- Secondary endpoints including: safety, time to PSA progression, time to next therapy, OS, PSA response, QoL

Hussain M, et al. ASCO GU 2018. Abstract 3.

ARAMIS trial design



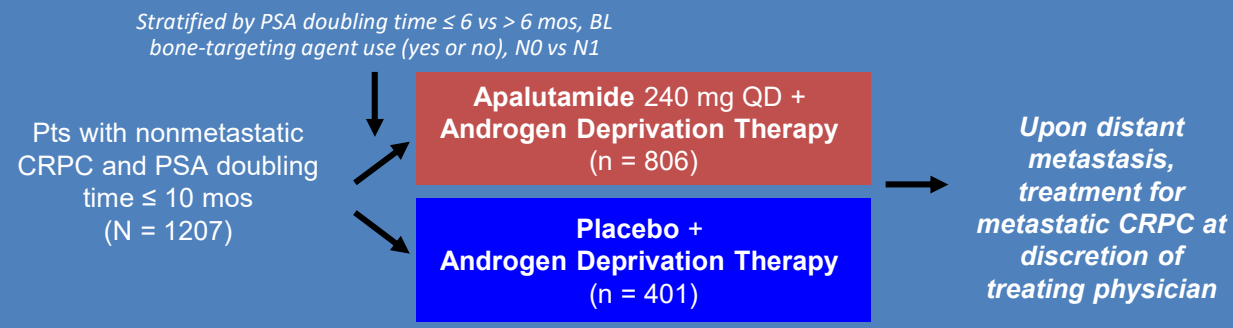
ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, non-metastatic castration-resistant prostate cancer; OS, overall survival; PSADT, prostate-specific antigen doubling time.

PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Presented by: Karim Fizazi

Presented By Karim Fizazi at 2019 Genitourinary Cancers Symposium

Apalutamide vs Placebo in Nonmetastatic CRPC (SPARTAN): Phase III Study Design



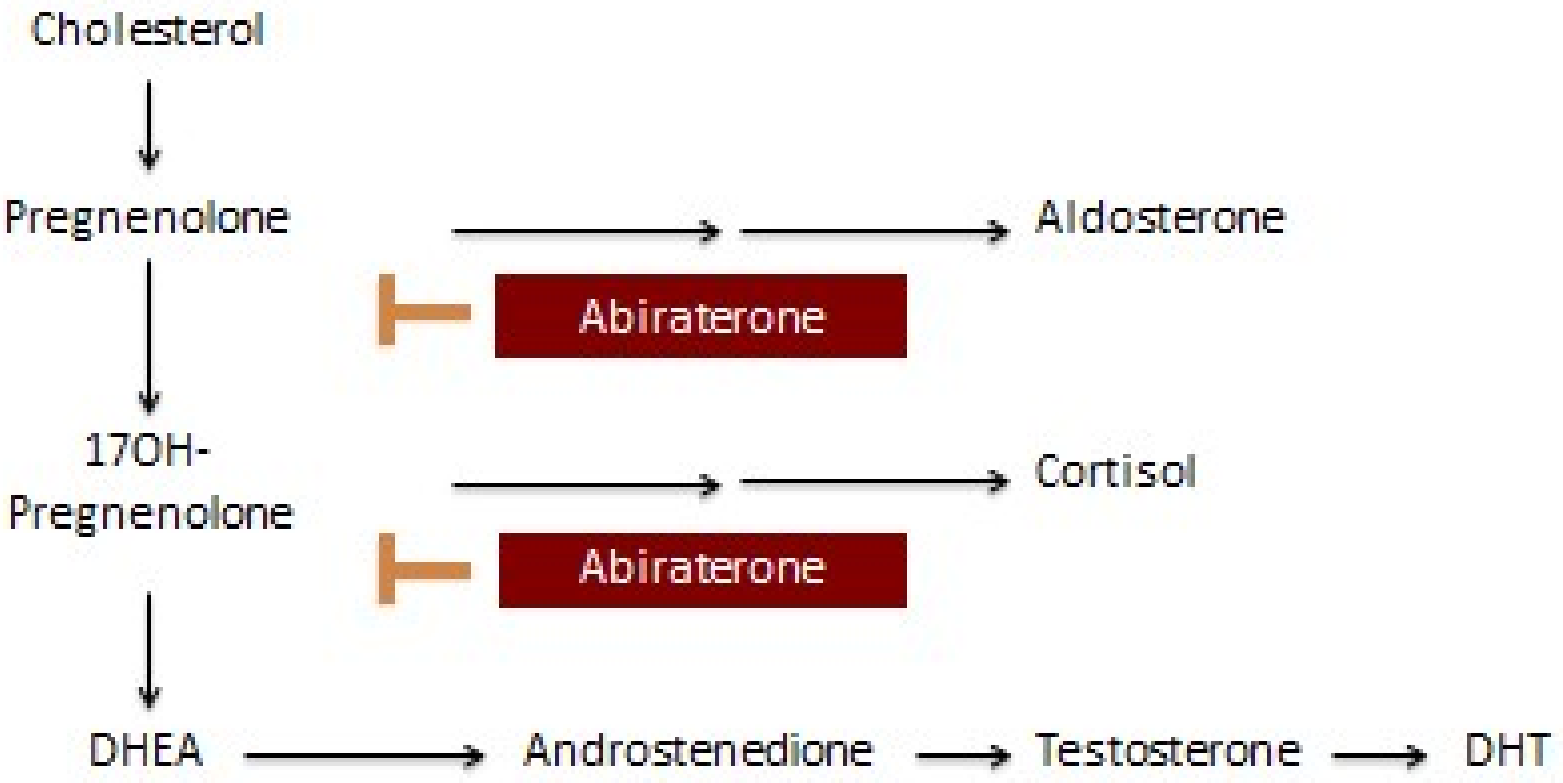
- Primary endpoint: metastasis-free survival
- Exploratory endpoints: time to PSA progression, PSA response rate, PFS, PRO
- Secondary endpoints including: time to metastasis, PFS, time to symptomatic progression, OS, time to chemotherapy

Small EJ, et al. ASCO GU 2018. Abstract 161. Smith MR, et al. N Engl J Med. 2018;[Epub ahead of print].

Next Generation Antiandrogens in Non-Metastatic Castration-Resistant Prostate Cancer

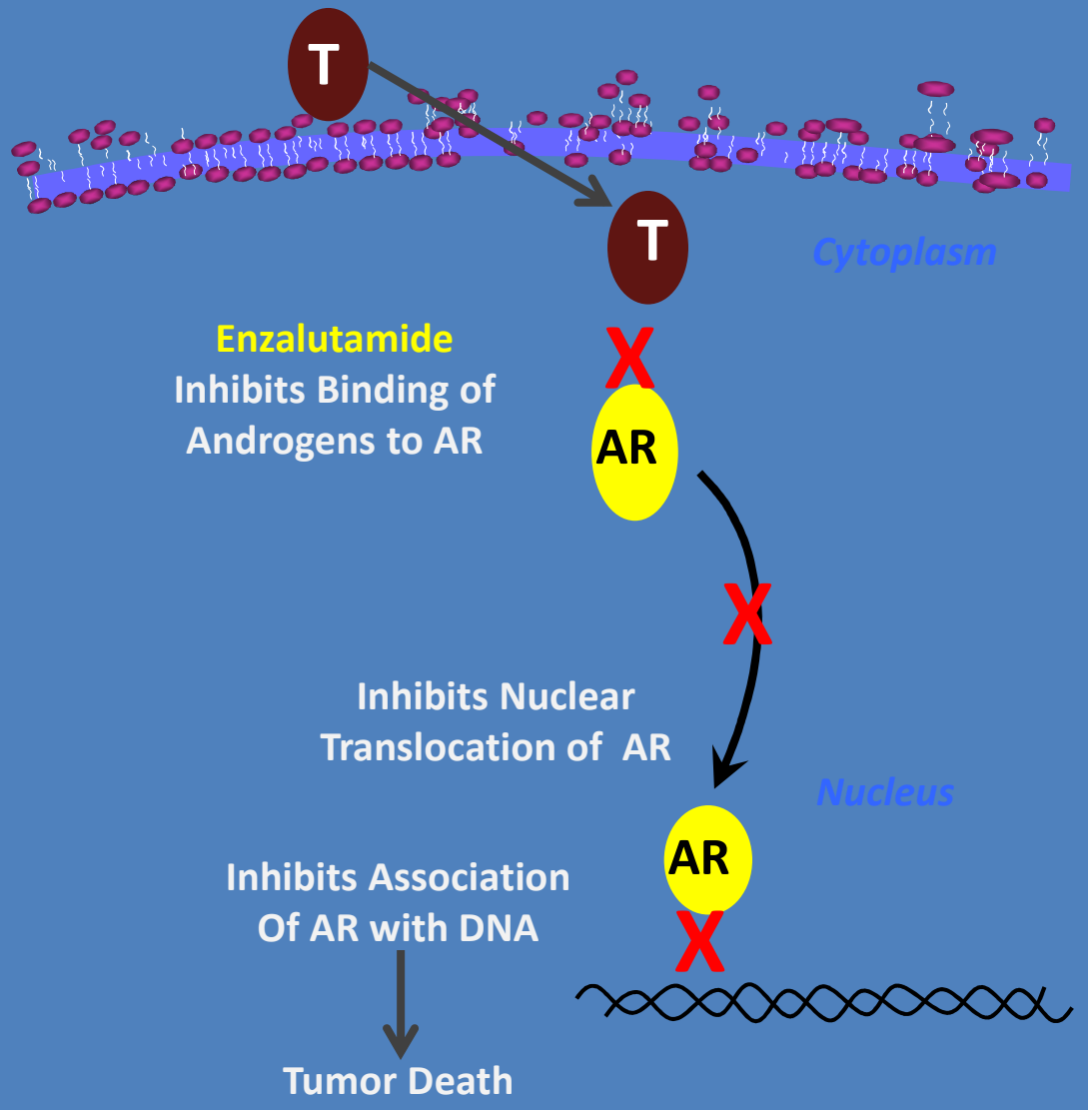
	PROSPER Enzalutamide	ARAMIS Darolutamide	SPARTAN Apalutamide
Metastases. Free Survival (Months)	36.6 vs 14.7 HR= 0.29	40.4 vs 18.4 HR=	40.5 vs 16.2 HR=0.28
Time to PSA Progression (Months)	37.2 vs 3.9	33.2 vs 7.3	Not reached vs 3.7
Duration of Treatment (Months)	18.4 vs 11.1	14.8 vs 11	Not Reported
Survival	HR 0.8; P=0.15	HR=0.71; P=0.71	HR 0.7 P=0.07

Abiraterone Acetate: Androgen Biosynthesis Inhibitor



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



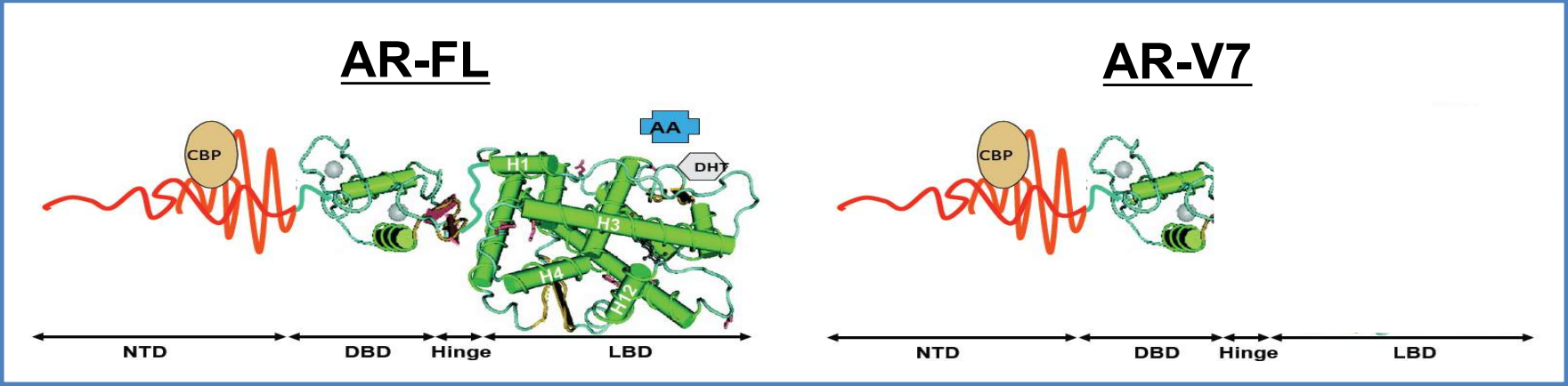
Tran C et al. *Science* 2009;324:787-790.

Abiraterone and Enzalutamide

- **There is clinical evidence of cross-resistance between abi and enza**
- **PSA responses to abi/enza after prior enza/abi are 10-20% and rPFS is 3-4 months** (Noonan KL et al. *Ann Oncol* 2013; 24:1802-7, Loriot Y et al. *Ann Oncol* 2013;24:1807-12, Schrader AJ et al. *Eur Urol* 2014;65:30-6, Badrising S et al. *Cancer* 2014;120:968-75, Cheng HH et al. PCAN 2015;18:122-7)
- **There is evidence of cross-resistance between abi/enza and taxanes**
- **Abi/enza are less effective after taxanes** (deBono JS et al *NEJM* 2011;364: 1995-2005, Scher HI et al *NEJM* 2012;367:1187-97, Nadal R et al *Prostate* 2014;74:1560-8), **and Taxanes are less effective after abi/enza** (Schweizer MT et al *Eur Urol* 2014;66:646-52, Mezynski J et al **Ann** Oncol 2012;23:2943-7)

AR-V7 Splice Variant Mutation

- **Androgen receptor variant-7 (AR-V7) is a truncated form of the AR that lacks the LBD, the target of *abiraterone enzalutamide, apalutamide, daralutamide* but remains constitutively active as a transcription factor**

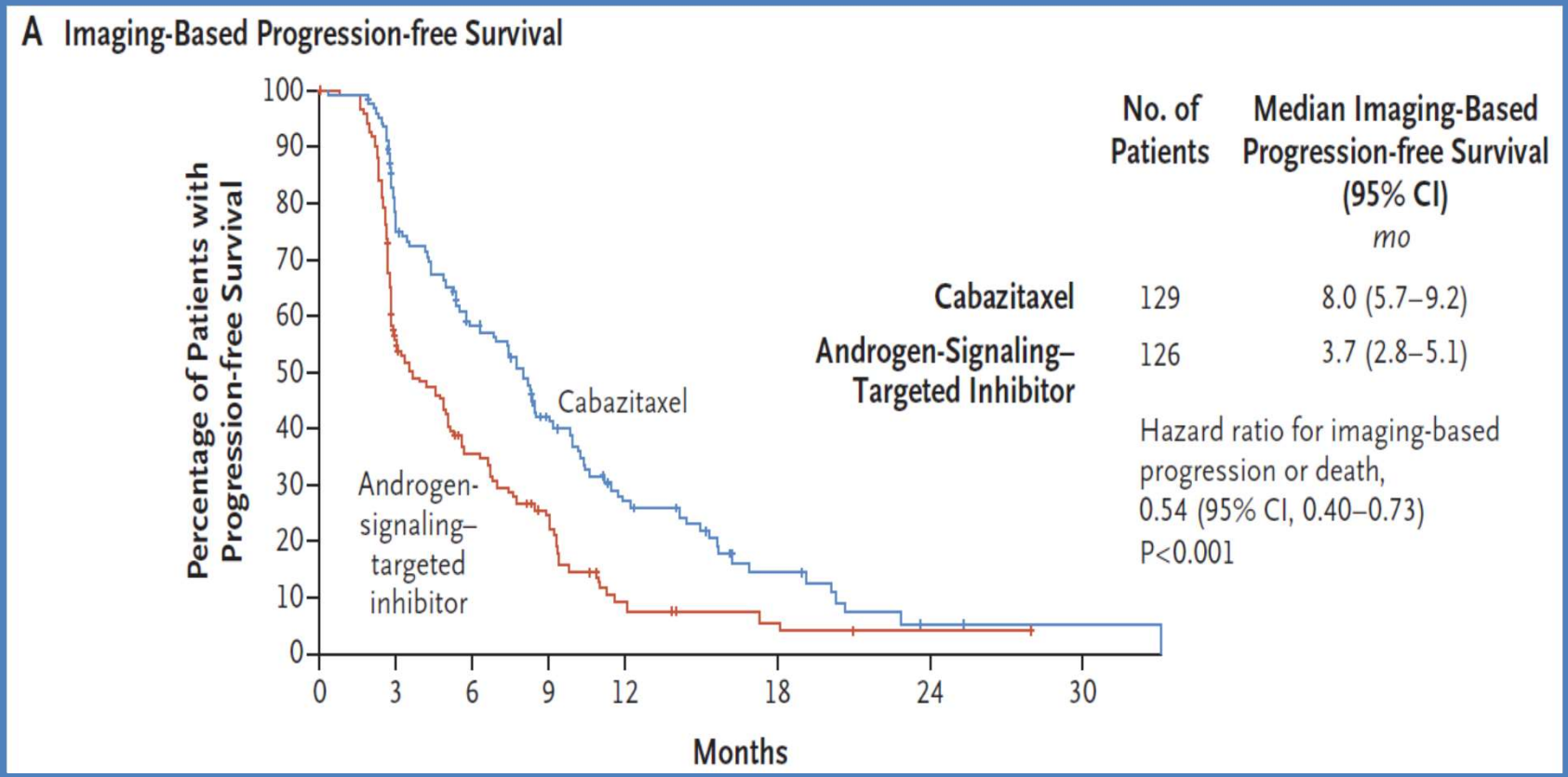


Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

R. de Wit, J. de Bono, C.N. Sternberg, K. Fizazi, B. Tombal, C. Wülfing, G. Kramer, J.-C. Eymard, A. Bamias, J. Carles, R. Iacovelli, B. Melichar, Á. Sverrisdóttir, C. Theodore, S. Feyerabend, C. Helissey, A. Ozatilgan, C. Geffriaud-Ricouard, and D. Castellano, for the CARD Investigators*

CABAZITAXEL VS ABIRATERONE OR ENZALUTAMIDE IN

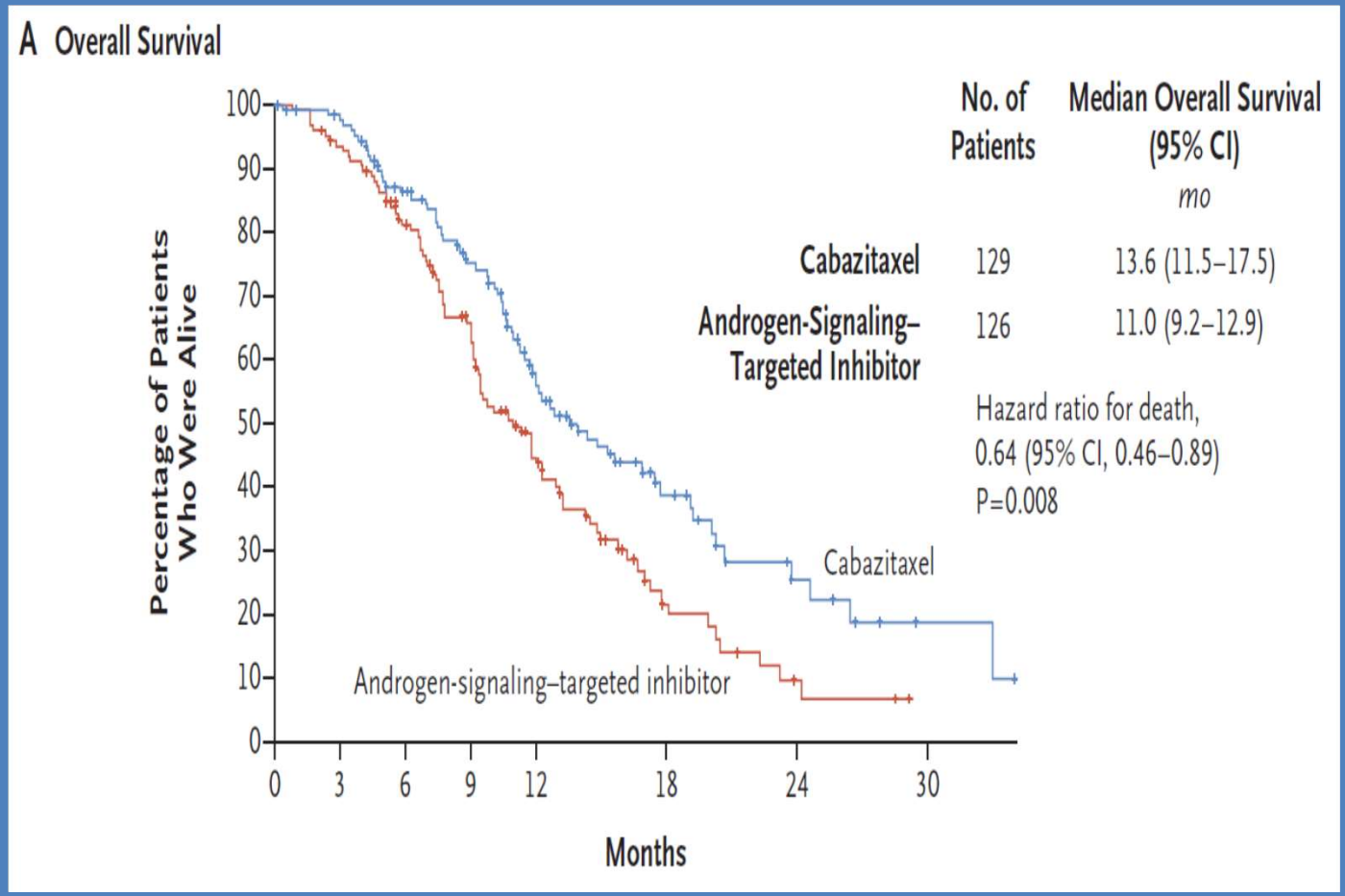
THE TREATMENT OF METASTATIC PROSTATE CANCER



R DE WIT : NEJM 2019: 2506-2518

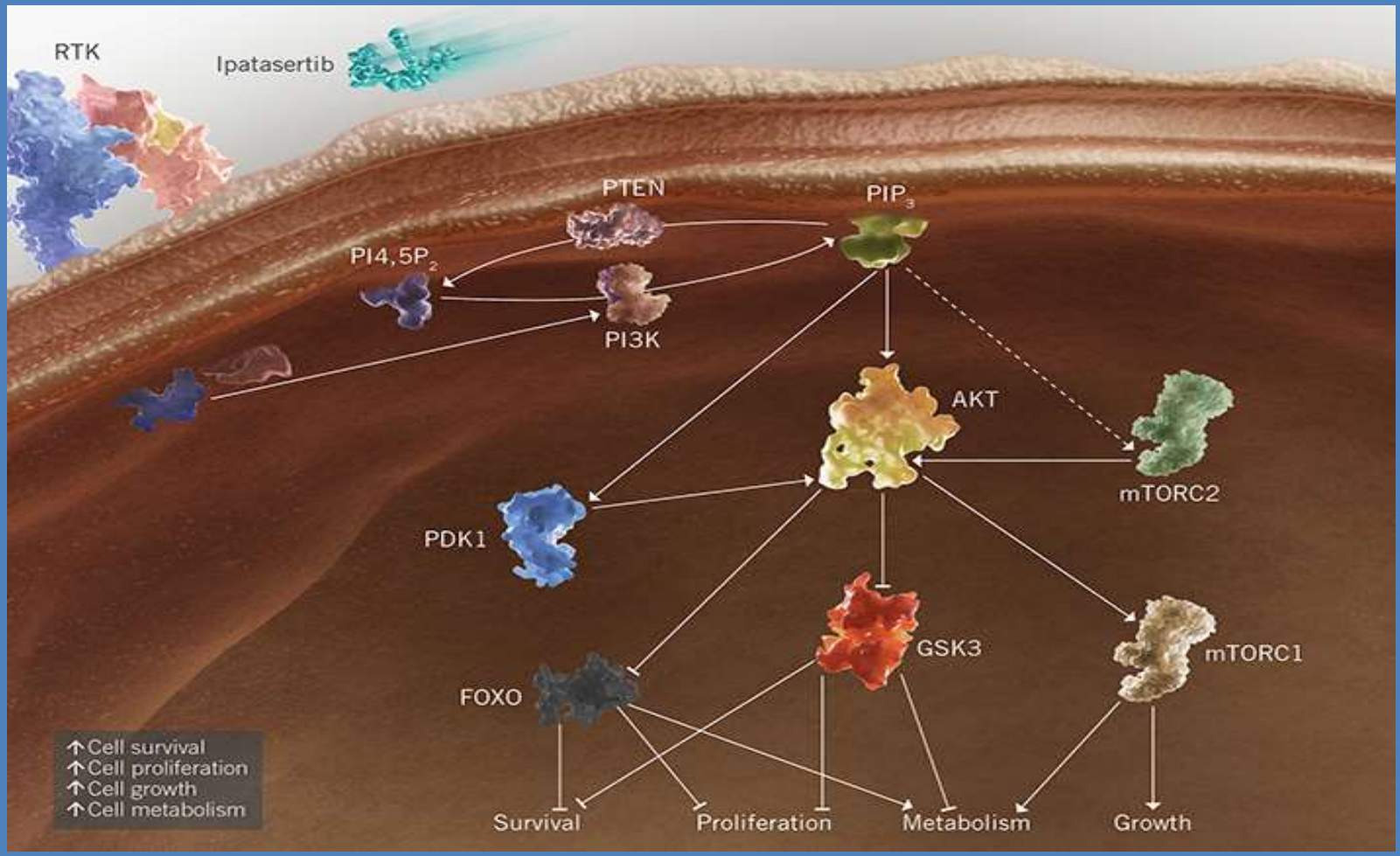
CABAZITAXEL VS ABIRATERONE OR ENZALUTAMIDE IN

THE TREATMENT OF METASTATIC PROSTATE CANCER



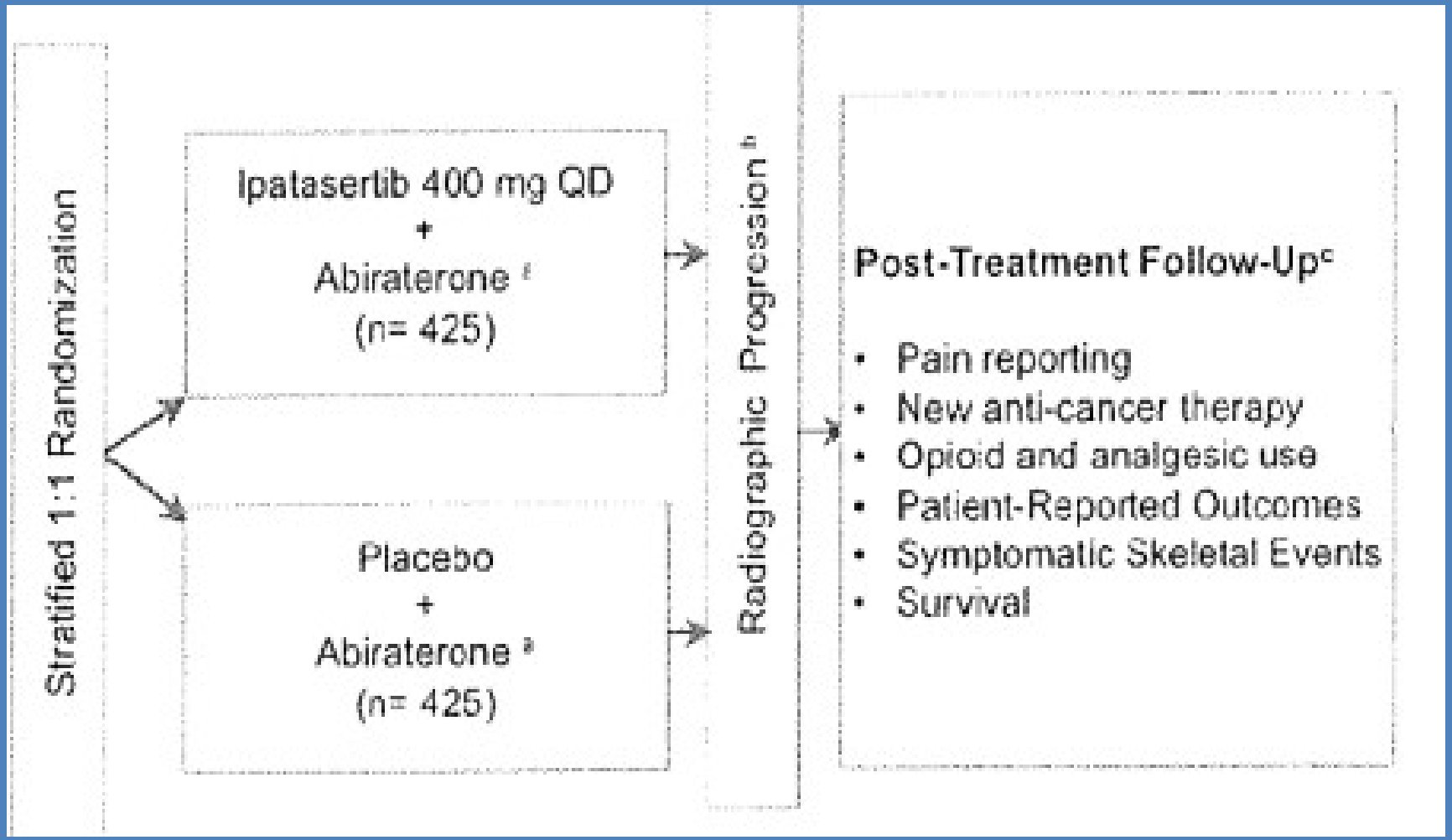
R DE WIT NEJM 2019; 381:2506-2518

Aberrant PI3-Aki-mTOR and AR signaling with PTEN loss is Common in mCRPC



Ipatasertib is an oral, investigational small molecule currently being studied for its potential to inhibit all 3 isoforms of AKT.[1,5]

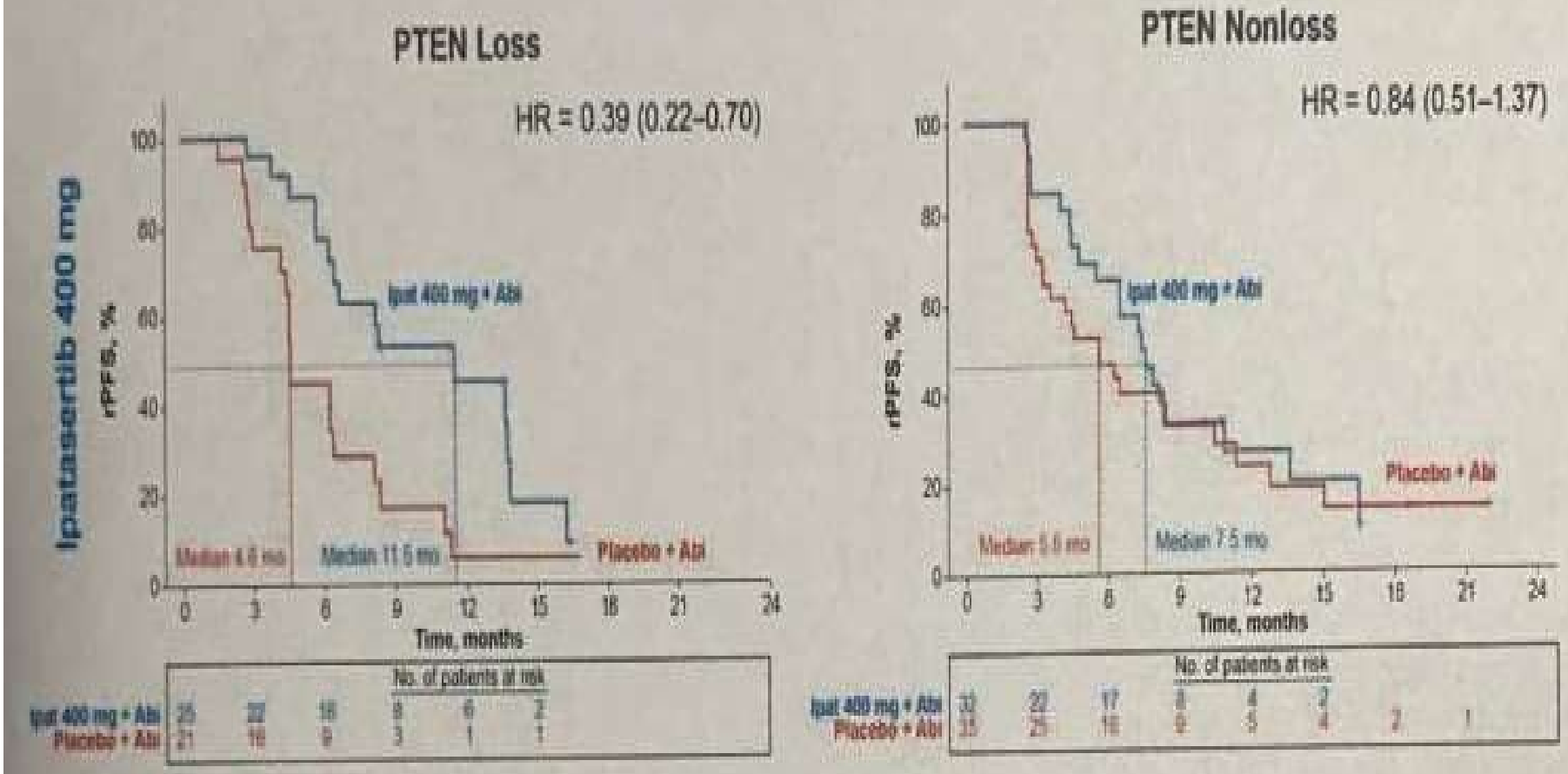
Phase 2 Clinical Trial of Abiraterone + Ipatasertib vs Abiraterone + Placebo in mCRPC Patients



Clinical Trial of Abiraterone + Ipatasertib vs Abiraterone in mCRPC Patients

Ipatasertib in Prostate Cancer with and without PTEN Loss

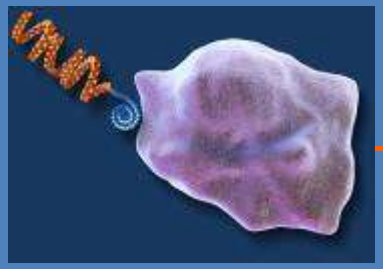
Results: rPFS: Comparison of PTEN Loss and Non-Loss



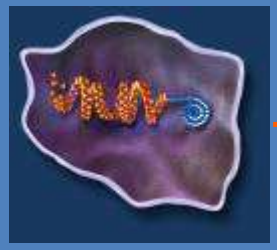
de Bono JS et al. Clin. Cancer Res 2019 Feb 1;25(3):928-936

Immunotherapeutic Treatment of Prostate Cancer

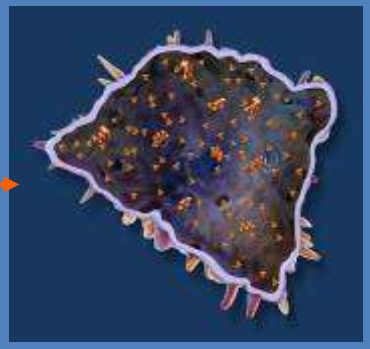
Sipuleucel-T: Autologous APC Cultured with PAP-cytokine Fusion Protein



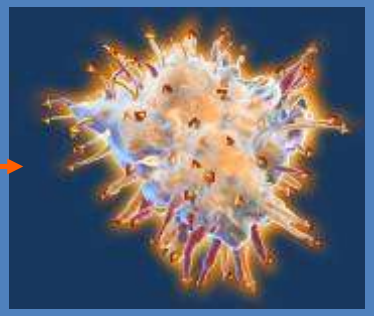
Recombinant Prostatic Acid Phosphatase (PAP) antigen combines with resting antigen presenting cell (APC)



APC takes up the antigen

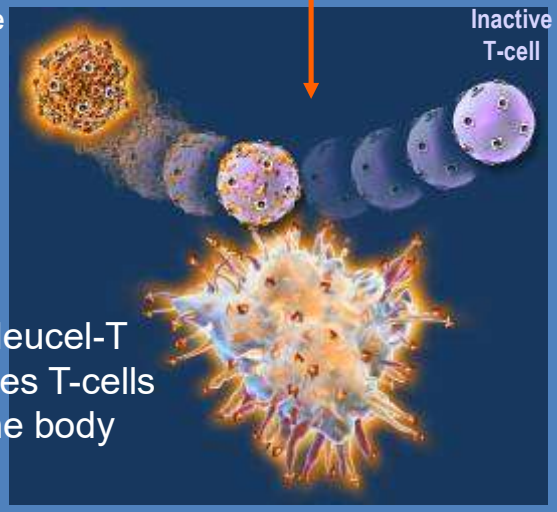


Antigen is processed and presented on surface of the APC

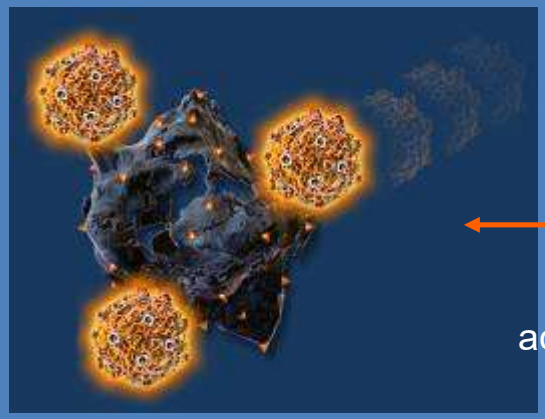


Fully activated, the APC is now sipuleucel-T

INFUSE PATIENT



Sipuleucel-T activates T-cells in the body

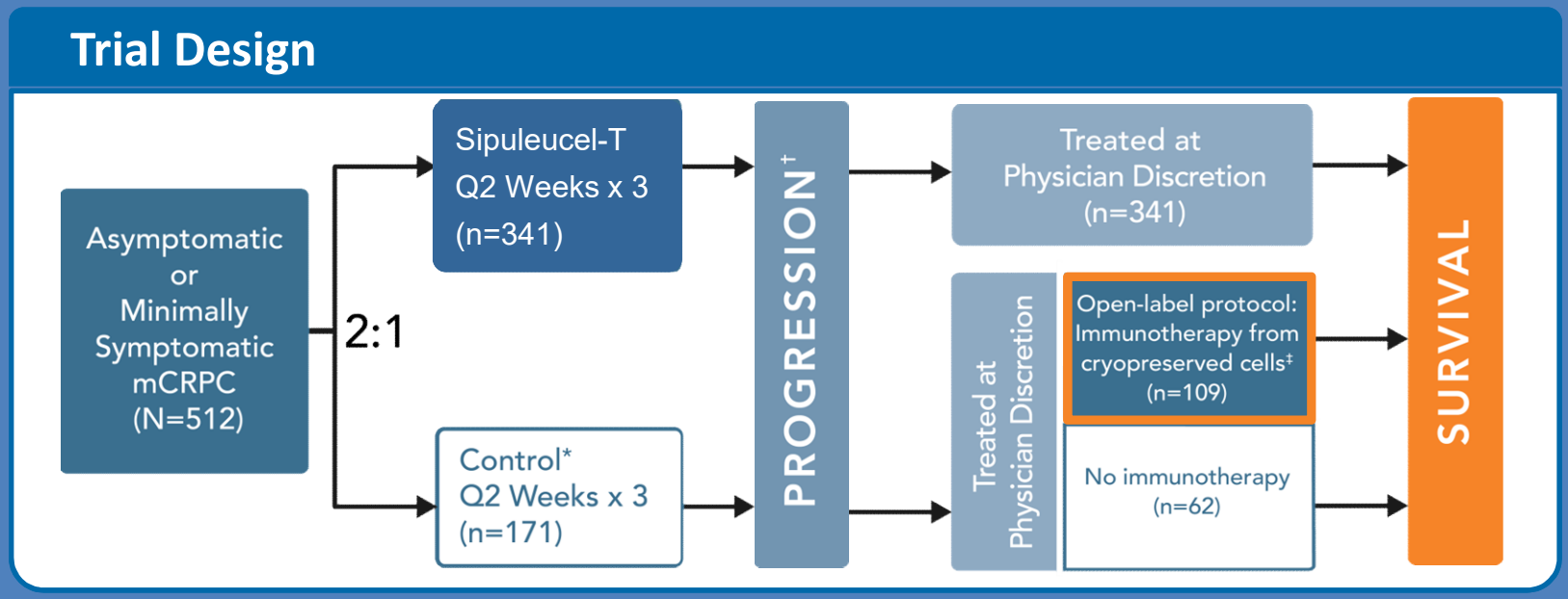


T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

IMPACT Trial Design

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



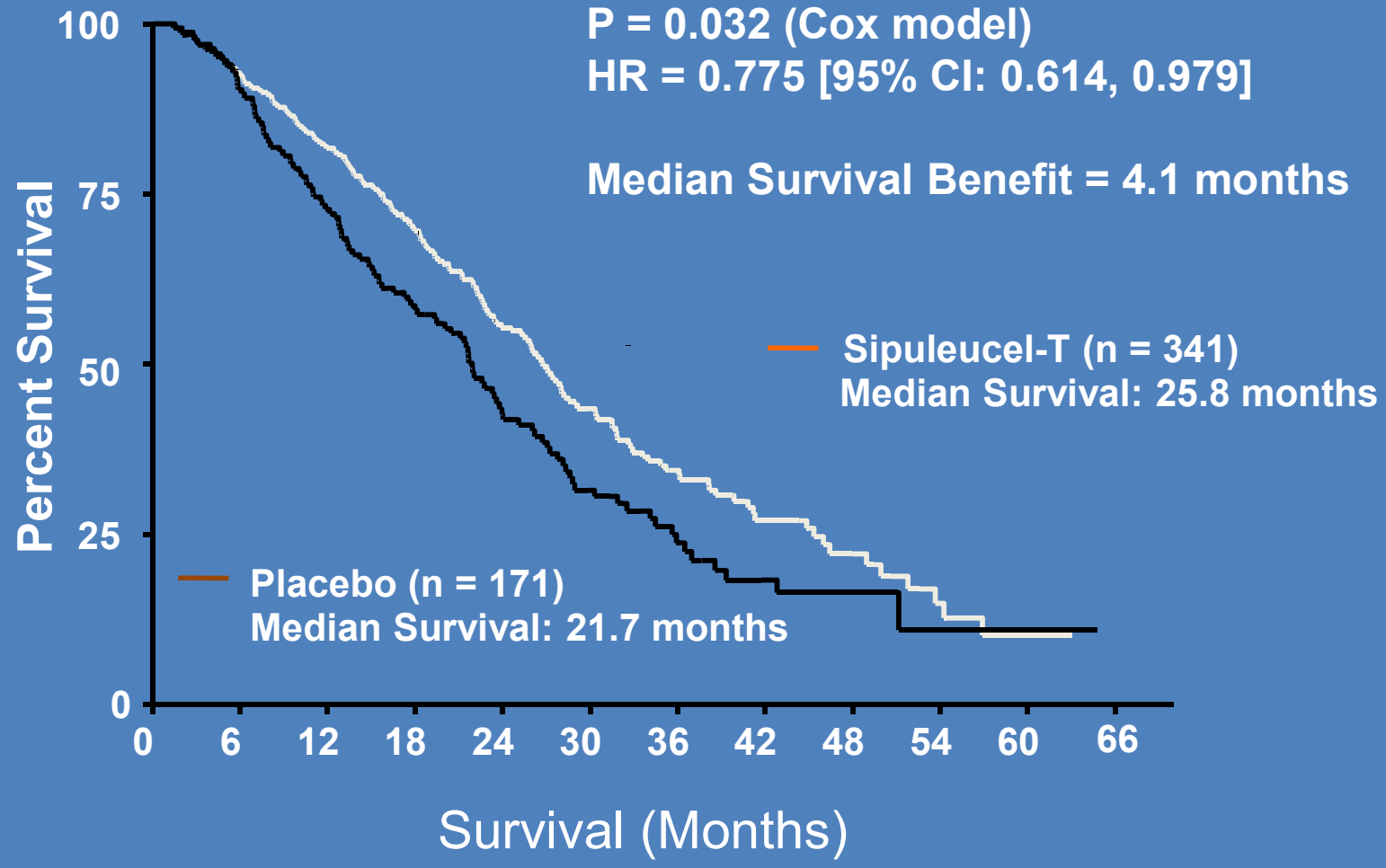
64% of patients in the control group, following progression, crossed over to a nonrandomized, open-label protocol

- 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.

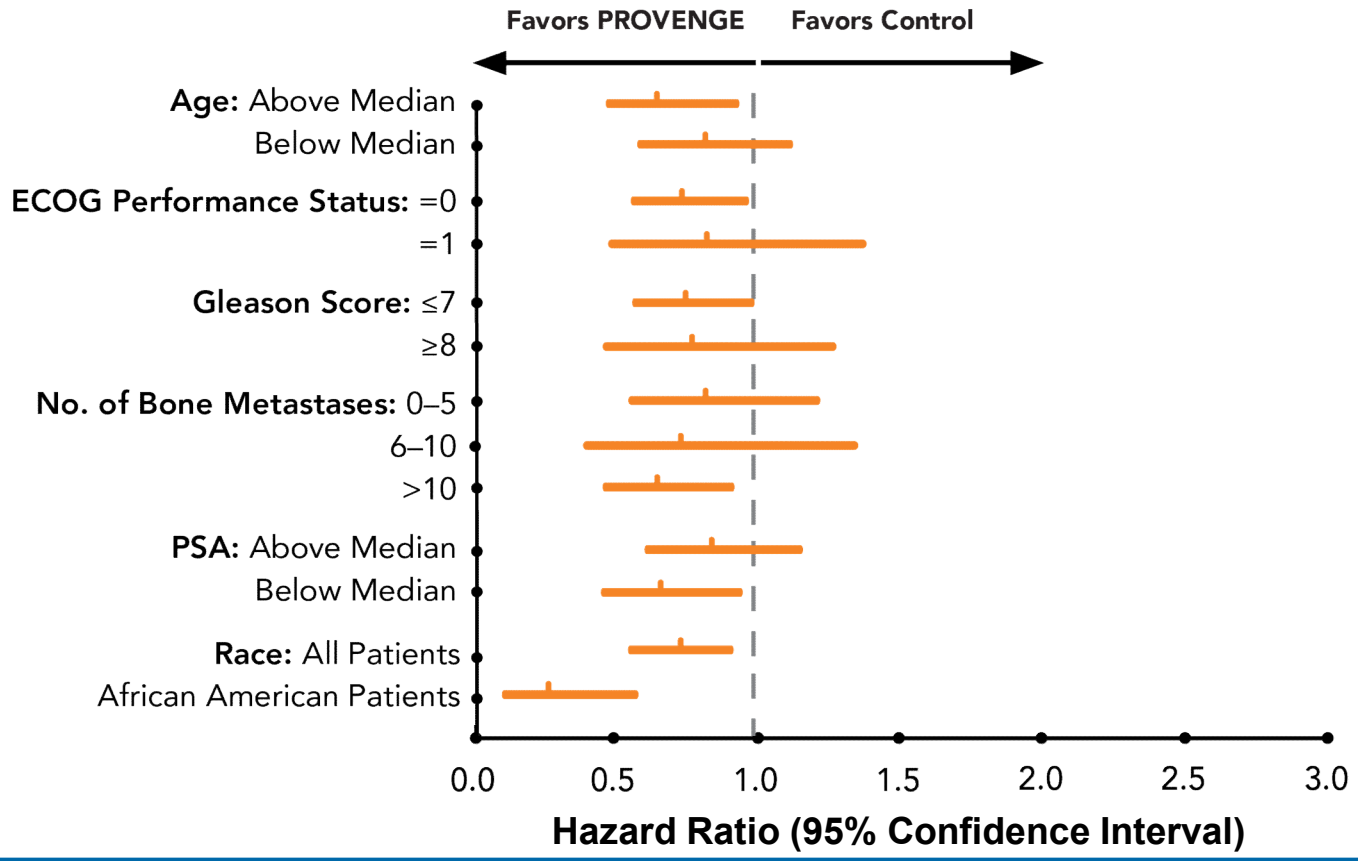
Kantoff PW et al. *N Engl J Med*. 2010;363:411-422.

IMPACT Overall Survival
Intent-to-Treat Population



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

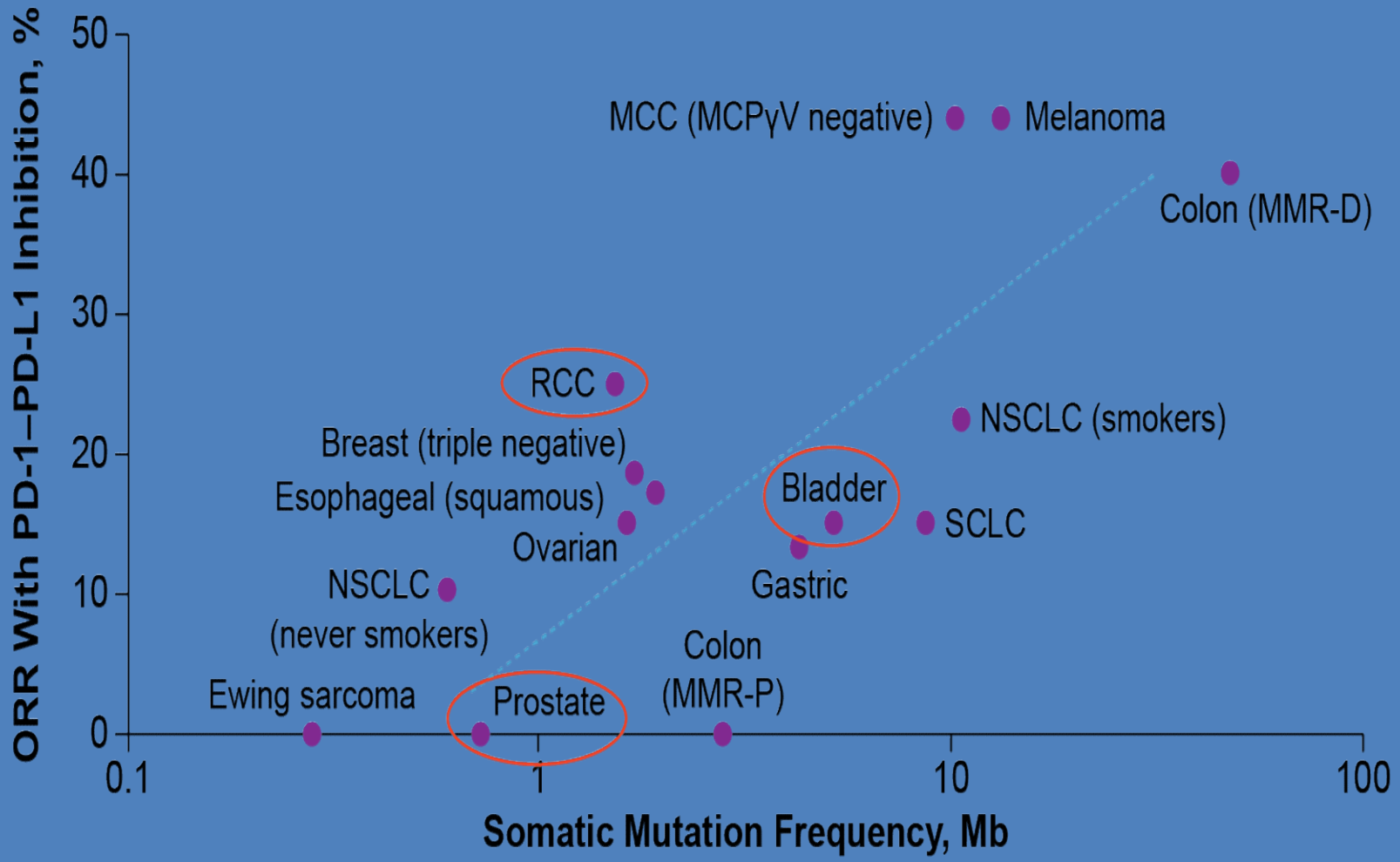
Patients in the lowest PSA quartile had greatest OS benefit with sipuleucel-T

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, months	13.0	7.1	5.4	2.8
HR	0.51	0.74	0.81	0.84
(95% CI)	(0.31 – 0.85)	(0.47 – 1.17)	(0.52 – 1.24)	(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)

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

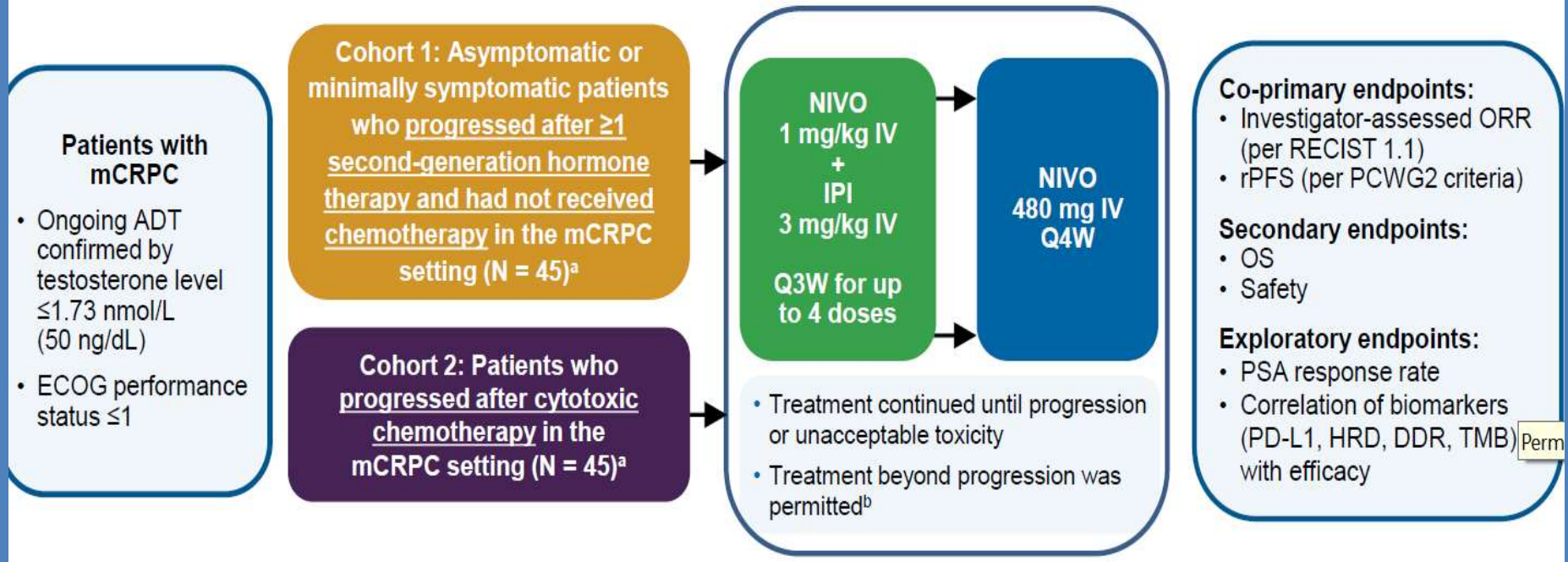
Response Rate and Tumor Mutational Burden



Yarchoan M et al. *Nature Rev Cancer*. 2017;17:209-222.

Study Design

Open-label, multicenter, phase 2 study (NCT02985957)



- Patients who had received ≥1 combination dose and who had toxicity that did not meet discontinuation criteria were permitted to begin NIVO maintenance before completion of all 4 combination doses

[a]In both cohorts, ≥30 patients were required to have measurable disease. [b]If the patient sustained clinical benefit while tolerating treatment, had stable performance status, and if continued treatment would not delay imminent interventions to prevent serious complications of progressive disease.
ADT, androgen deprivation therapy; DDR, DNA damage repair; HRD, homologous recombination deficiency; PCWG2, Prostate Cancer Working Group 2; rPFS, radiographic PFS; TMB, tumor mutational burden.

Exploratory Biomarker Analyses: Gene Panels

- HRD: 15 genes
  - ***ATM***, *BARD1, BRCA1,* ***BRCA2***, *BRIP1,* ***CDK12***, *CHEK2,* ***FANCA***, *NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*
- DDR: 48 genes, <u>including 13 from HRD</u>
  - Nucleotide excision repair: ***ERCC2***, ***ERCC3***, *ERCC4, ERCC5, ERCC6*
  - Homologous recombination: *BRCA1,* ***BRCA2***, *RAD50, RAD51, RAD51B, RAD51C, RAD52, RAD54L, NBN, MRE11A, RAD51D, CTIP*
  - DNA sensor: ***ATM***, ***ATR***, *MDC1,* ***ATRX***, *CHEK1, CHEK2*
  - Fanconi anemia pathway: *PALB2, BRIP1,* ***FANCA***, ***FANCB***, *FANCC, FANCD2, FANCE, FANCF, FANCG, BLM*
  - Base excision repair: ***XRCC2***, *XRCC3, XRCC4, XRCC5, XRCC6*
  - Mismatch repair: ***MLH1***, *MLH3, MSH2, MSH6, PMS2*
  - Other: *MUTYH, RECQL4,* ***POLQ***, *POLE,* ***WRN***

All bolded genes were present in patients in this study; red bolded genes were present in patients with objective response

Ipilimumab + Nivolumab
Exploratory Biomarker Subset Analysis

ORR were higher in patients with greater

PDL-1 mutational rate (>1%)

DNA Damage Repair (DDR) -- Microsatellite Instability (MSI)

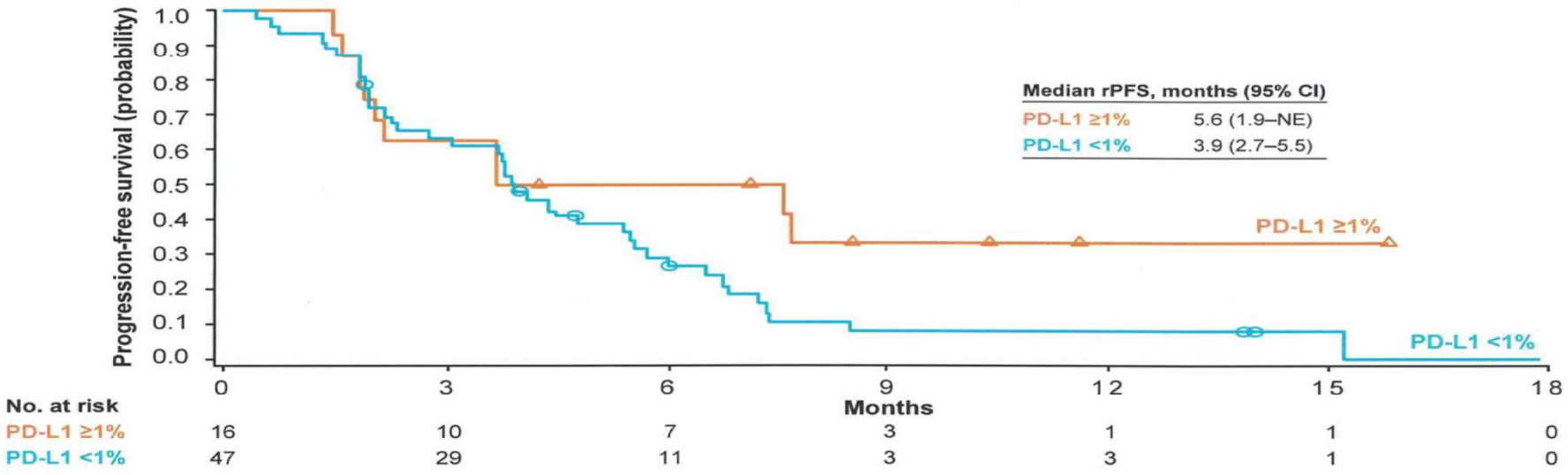
Homologous Recombination Deficiency (HRD)

Above mediation tumor mutation burden

Phase 2 Study of Nivolumab + Ipilimumab for the Treatment of mCRPC

CheckMate 650

rPFS by PD-L1: Cohort 1 (Chemo-naïve) and Cohort 2 (Chemo-experienced) Combined



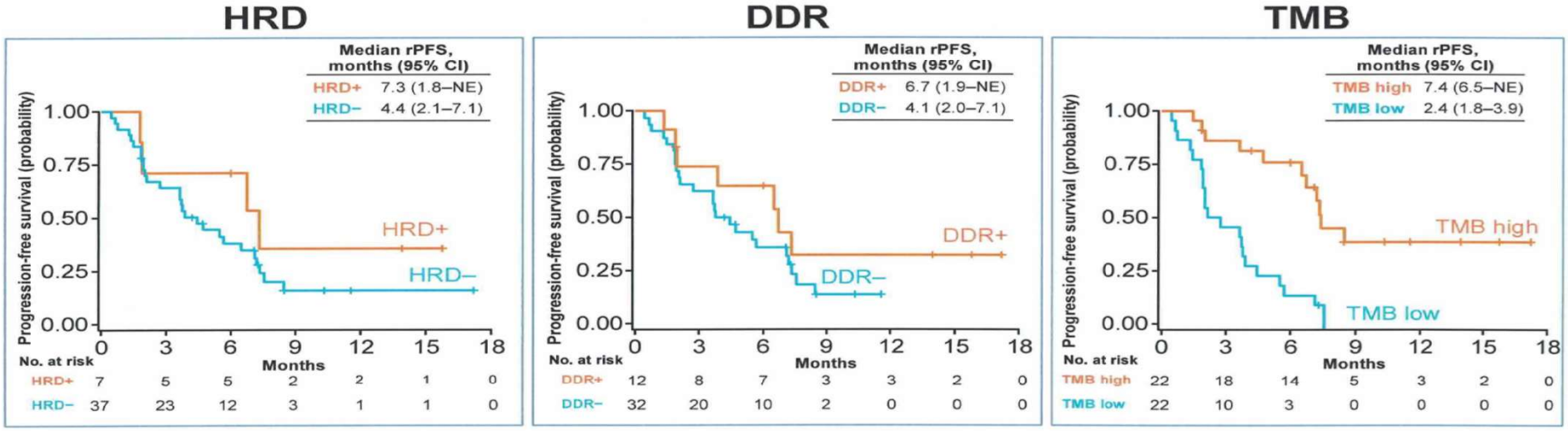
- Patients with PD-L1 ≥1% had numerically longer median rPFS versus patients with PD-L1 <1%

NE, not estimable.

Phase 2 Study of Nivolumab + Ipilimumab for the Treatment of mCRPC

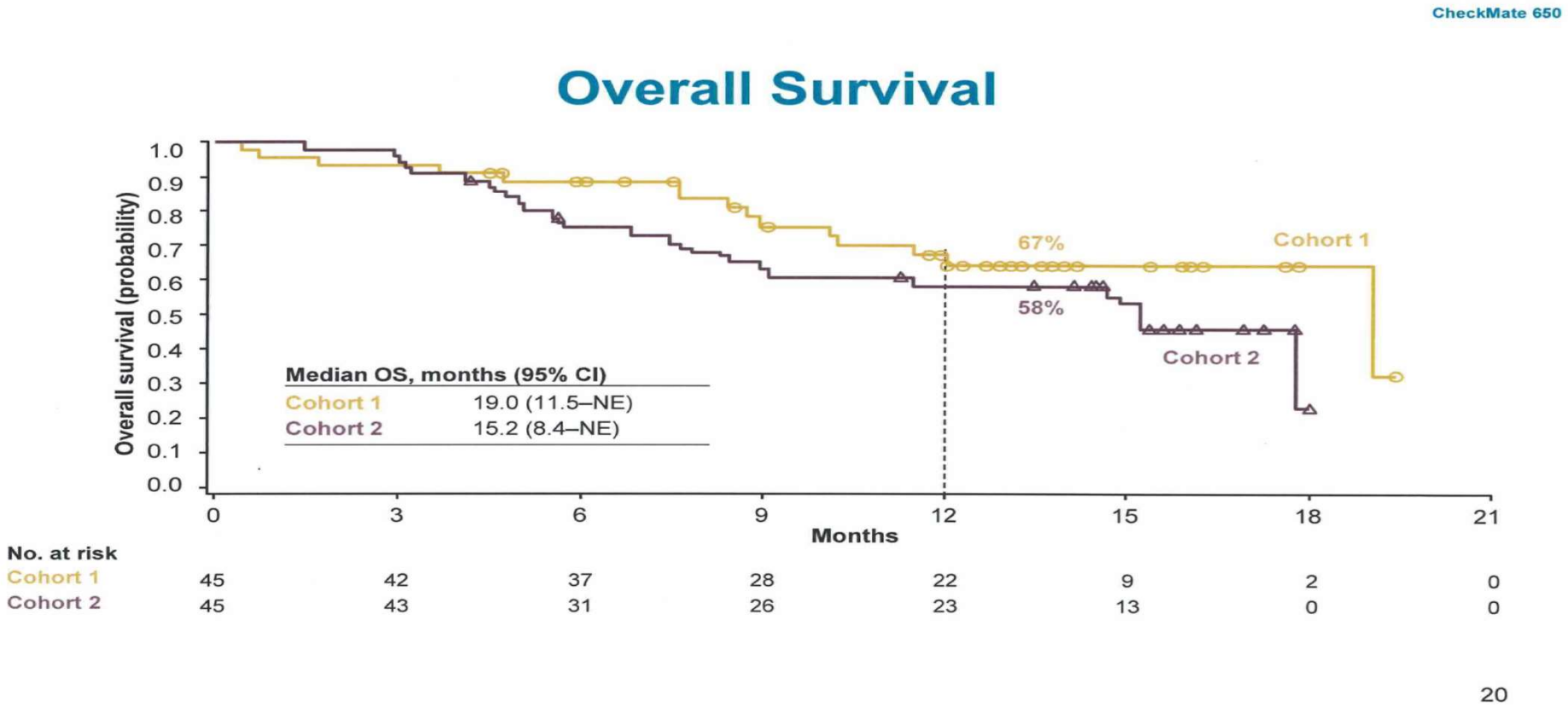
CheckMate 650

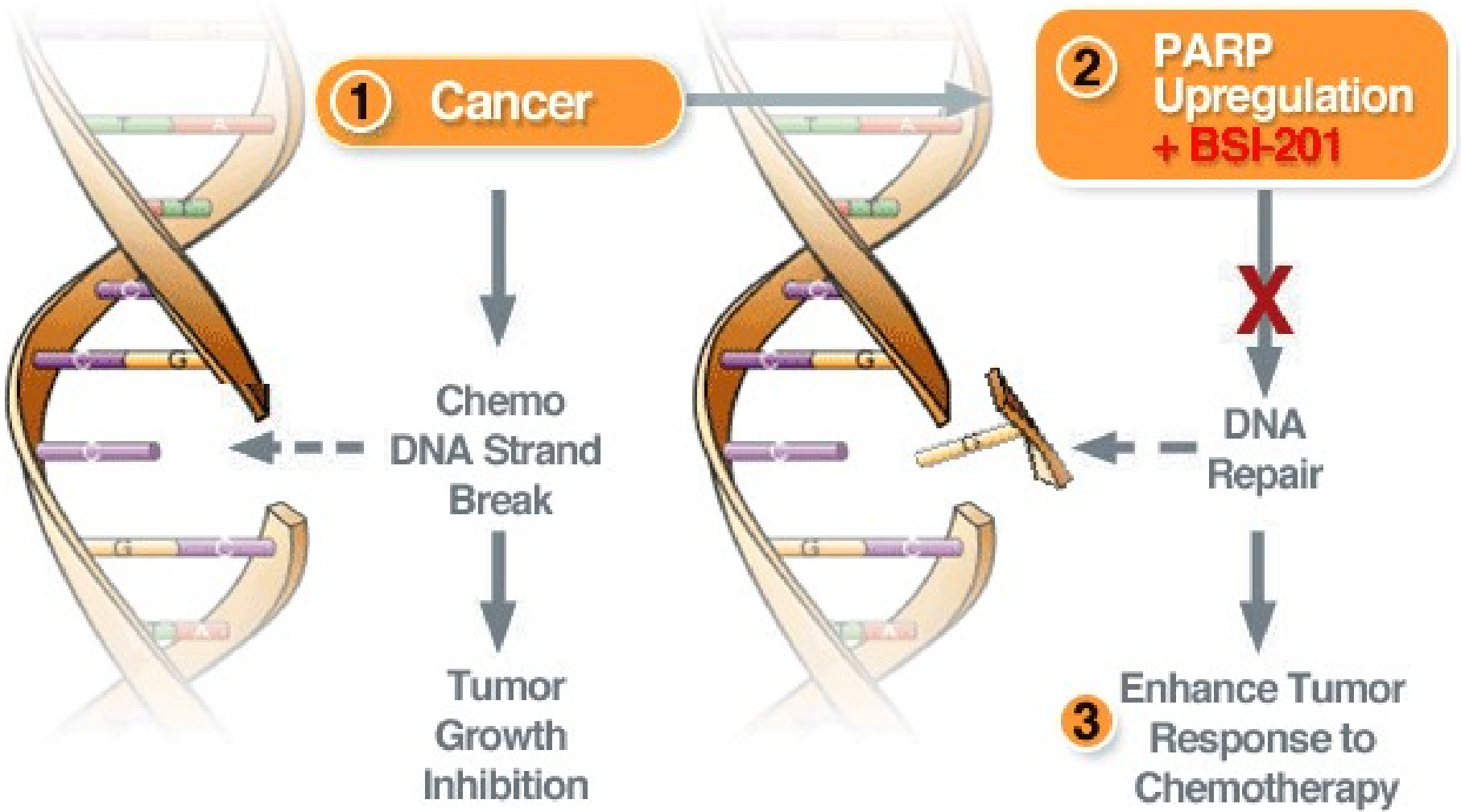
rPFS by HRD, DDR and TMB: Cohort 1 (Chemo-naïve) and Cohort 2 (Chemo-experienced) Combined



- Patients with HRD+ or DDR+ tumors had numerically longer median rPFS
- High TMB (above median) was associated with prolonged rPFS vs low TMB (below median) ($P < 0.0001$)

Phase 2 Study of Nivolumab plus Ipilimumab for the Treatment of mCRPC



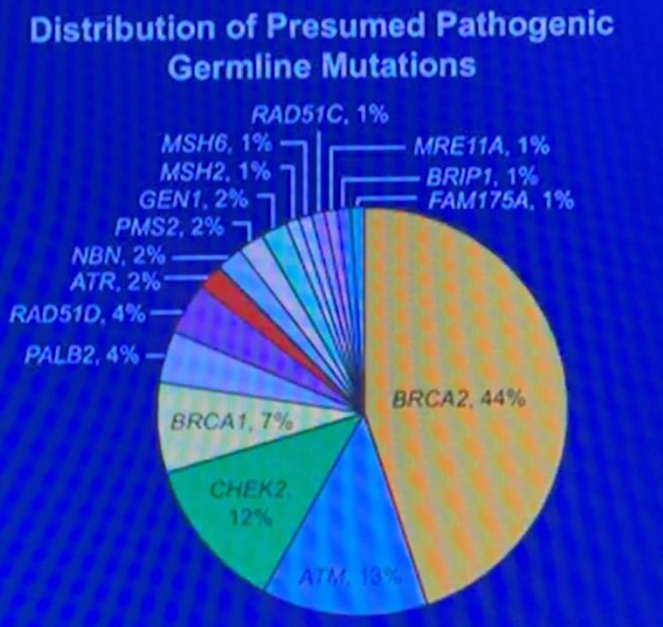


1. Many commonly utilized cancer chemotherapy regimens target tumor cells via fatal DNA lesions
2. Key DNA repair pathways (such as PARP) are upregulated in tumor cells - may lead to resistance
3. Inhibiting PARP may potentiate chemotherapy or be used as monotherapy in conditions with pre-existing DNA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

Pathogenic Germline Mutations in Prostate Cancer

1 in 10 Men With Metastatic Prostate Cancer Have Germline DNA Repair Mutations

- 11.8% of 692 men with mPC found to have germline DNA repair defects
- Can represent autosomal dominant cancer predisposition (eg, *BRCA2*, *BRCA1*)
- Not all men with germline mutations had a family history of cancer



Pritchard CC, et al. N Engl J Med. 2016;375:443-453.

Slide courtesy of Heather Cheng

Recommendations for Germline Genetic Testing/Counseling in Prostate Cancer

- Recommendations continue to evolve with many questions remaining
- In general, germline genetic testing should be offered to pts with:
  - Metastatic prostate cancer
  - Known mutation in a cancer susceptibility gene within the family
  - Family history suggestive of hereditary prostate cancer syndrome, hereditary breast and ovarian cancer syndrome, or Lynch syndrome
  - Tumor (somatic) sequencing indicating presence of mutations in hereditary cancer risk genes (eg, *BRCA2*, *BRCA1*, *ATM*, *MSH2*, *MSH6*, *MLH1*, *PMS2*)
  - High risk localized disease

Gillessen S, et al. Ann Oncol. 2015;26:1589-1604. Giri VN, et al. J Clin Oncol. 2017

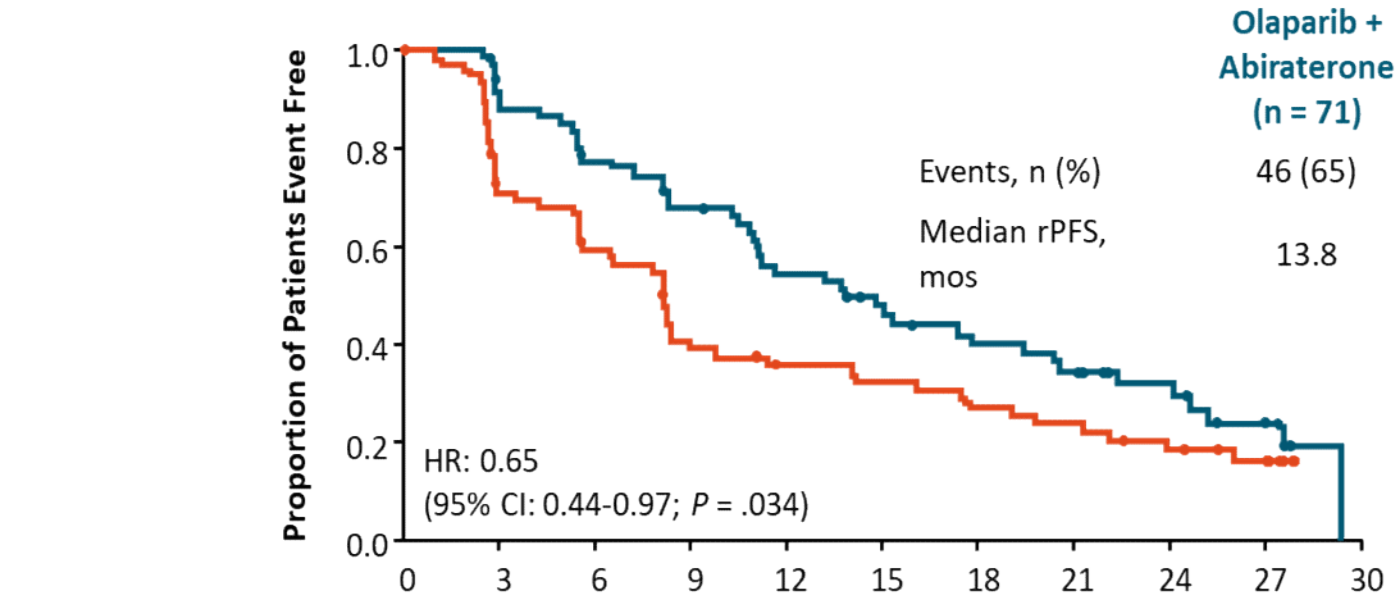
Olaparib + Abiraterone in mCRPC: Background

- Olaparib: PARP inhibitor approved by FDA for treatment of recurrent ovarian cancer and previously treated, germline *BRCA*-mutated advanced ovarian cancer or metastatic breast cancer[1]
- In phase II TOPARP-A trial, olaparib monotherapy demonstrated antitumor activity in patients with previously treated mCRPC, particularly those with DNA-repair defects[2]
- Combination of olaparib + abiraterone may provide synergistic antitumor activity due to increased sensitivity to PARP inhibition resulting from functional HRR impairment via ADT[3-5]
- Current study evaluated efficacy, safety of olaparib + abiraterone in patients with mCRPC following chemotherapy regardless of HRR mutation status[6
-]

1.

Olaparib [package insert]. 2. Mateo J, et al. N Engl J Med. 2015;373:1697-1708. 3. Schiewer MJ, et al. Cancer Discov. 2012;2:1134-1149. 4. Polinghorn WR, et al. Cancer Discov. 2013;3:1245-1253. 5. Asim M, et al. Nat Commun. 2017;8:374. 6. Clarke N, et al. ASCO 2018. Abstract 5003.

Olaparib + Abiraterone vs Abiraterone Metastatic CRPC -- rPFS

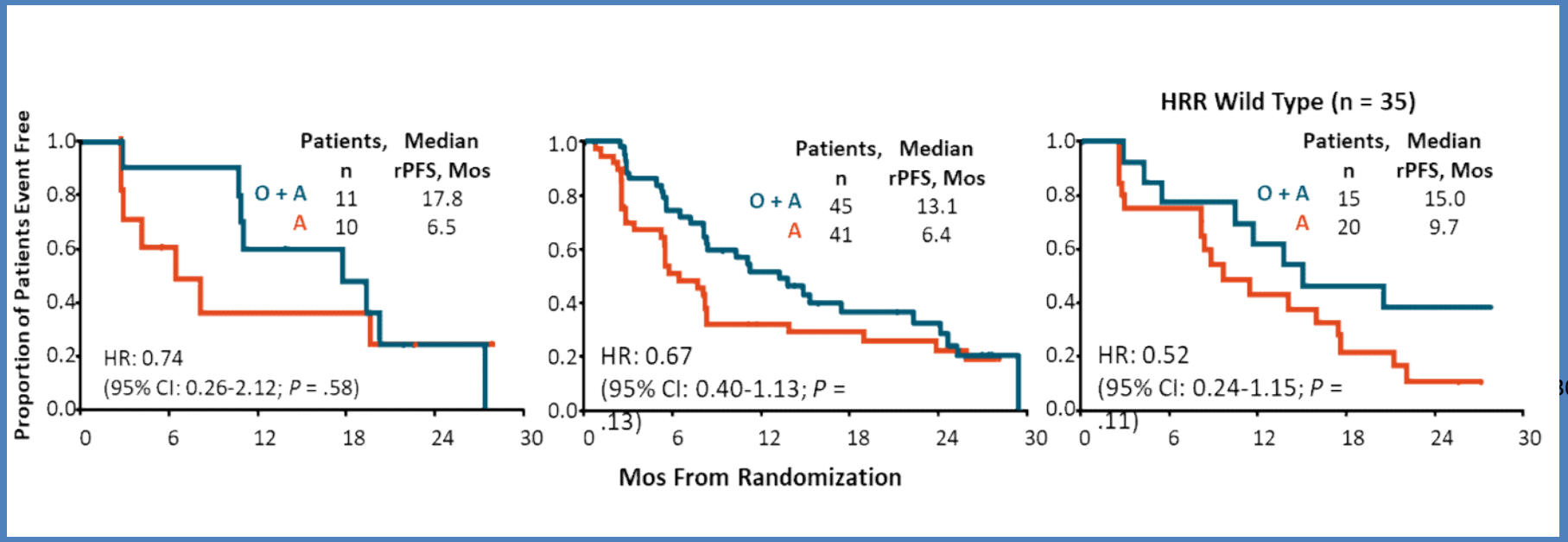


	Olaparib + Abiraterone (n = 71)	Abiraterone (n = 71)
Events, n (%)	46 (65)	54 (76)
Median rPFS, mos	13.8	8.2

Patients at Risk, n											
Olaparib + abiraterone	71	58	50	42	33	26	21	18	13	8	0
Abiraterone	71	48	39	25	21	19	16	14	10	7	0

Clarke N, et al. ASCO 2018. Abstract 5003. Reproduced with permission.

Olaparib + Abiraterone vs Abiraterone Metastatic CRPC – radiographic PFS



Olaparib + Abiraterone in mCRPC: Conclusions

- In patients with mCRPC previously treated with docetaxel, addition of olaparib to abiraterone significantly increased radiologic PFS vs abiraterone alone
  - HR: 0.65 (95% CI: 0.44-0.97; *P* = .034)
  - Benefit seen regardless of HRR mutation status
- Increased toxicity with combination, including serious cardiovascular AEs
- Phase III trial ongoing

Objectives for Genetic Testing

Somatic (Tumor) Testing

Tests mutation status of MULTIPLE genes within one sample (tumor or ctDNA)

Not yet standardized reporting

Treatment and potential heritability implications

(Assay variance; less sensitive and less specific)

Germline Testing

Tests mutation status of SINGLE or defined subset of genes with one sample (blood or saliva)

More standardized reporting

Heritability and potential treatment implications

(but will miss somatic-only mutations)

Treatment-Related Adverse Events[a]

Event	Cohort 1 (N = 45)		Cohort 2 (N = 45)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Any treatment-related AE, %	93.3	42.2	95.6	53.3
Most common treatment-related AEs[b], %				
Diarrhea	37.8	6.7	53.3	11.1
Fatigue	33.3	2.2	44.4	0
Maculo-papular rash	20.0	0	22.2	2.2
Rash	20.0	4.4	15.6	2.2
Nausea	15.6	0	24.4	2.2
Pruritis	15.6	0	8.9	0
Hypothyroidism	13.3	0	15.6	0
Decreased appetite	11.1	0	35.6	0
Pyrexia	11.1	0	8.9	0
Colitis	8.9	4.4	17.8	11.1
Vomiting	8.9	2.2	17.8	4.4
Any treatment-related AE leading to DC, %	33.3	31.1	35.6	26.7
Treatment-related deaths	n = 2[c]		n = 2[d]	

[a]Includes events reported between first dose and 30 days after last dose. [b]Any grade events reported in at least 10% of all patients. [c]One patient had grade 5 treatment-related sudden death after the 4th dose; one patient had grade 4 treatment-related myocarditis with fatal outcome after 1st dose. [d]One patient had grade 4 treatment-related septic shock with fatal outcome after the 2nd dose; one patient had grade 4 treatment-related interstitial lung disease with fatal outcome after the 4th dose.
DC, discontinuation.

PSMA -Targeted Therapy

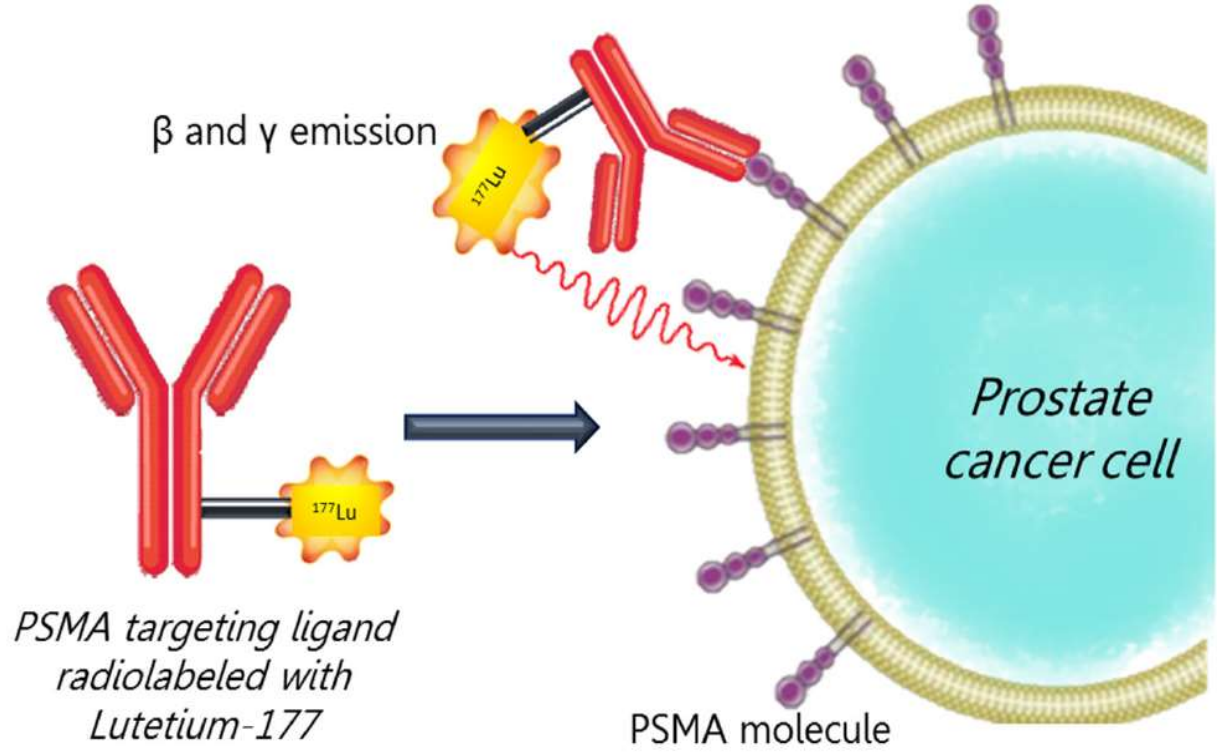
- **PSMA is an active target for prostate cancer**

- Can we bridge T cells to prostate tumor cells with a molecule that binds to both “Bispecific T cell engager” (BiTE) aka “molecular glue”?

- **Preliminary evidence for activity**
  -16 patients, varying dose levels (phase 1), virtually all had prior docetaxel and abiraterone/enzalutamide
  - 3 patients with partial tumor shrinkage
  - Dose dependent PSA decreases: 3 of 9 patients had >=50% PSA reductions at 3 highest doses

- **Difficult therapy**
  - Continuous infusion (24/7)
  - Almost ½ of patients developed infections (indwelling catheter)

Binding of Radiolabeled (Lu177) PSMA Targeting Ligand to PSMA On Prostate Cancer Cell



The targeting ligand binds to PSMA on prostate cancer cells. Once bound to the neoplastic cell, 177Lu atom releases energetic β and γ particles. This results in a DNA-damaging radiation.

FIGURE 3 | The targeting ligand binds to PSMA on prostate cancer cells. Once bound to the neoplastic cell, 177Lu atom releases an energetic beta and gamma particles that results in a DNA-damaging radiation.

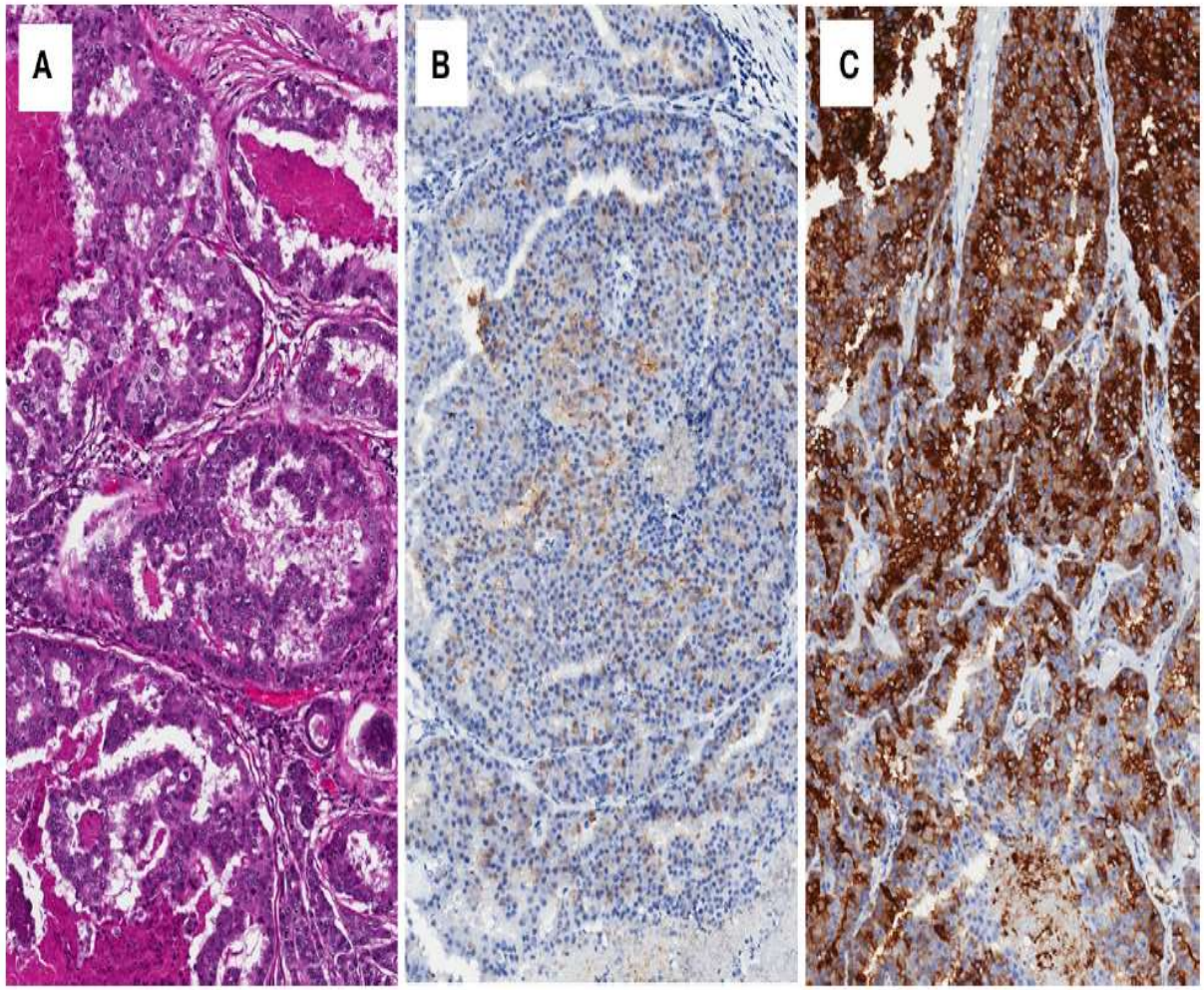


FIGURE 1 | Brain metastasis of prostate cancer with cribriform pattern **(A)**, showing low expression of PSA **(B)**, and intense expression of PSMA **(C)**.

PSMA-BASED IMAGING for DIAGNOSING PRIMARY PROSTATE CANCER

Cimadamore et al.

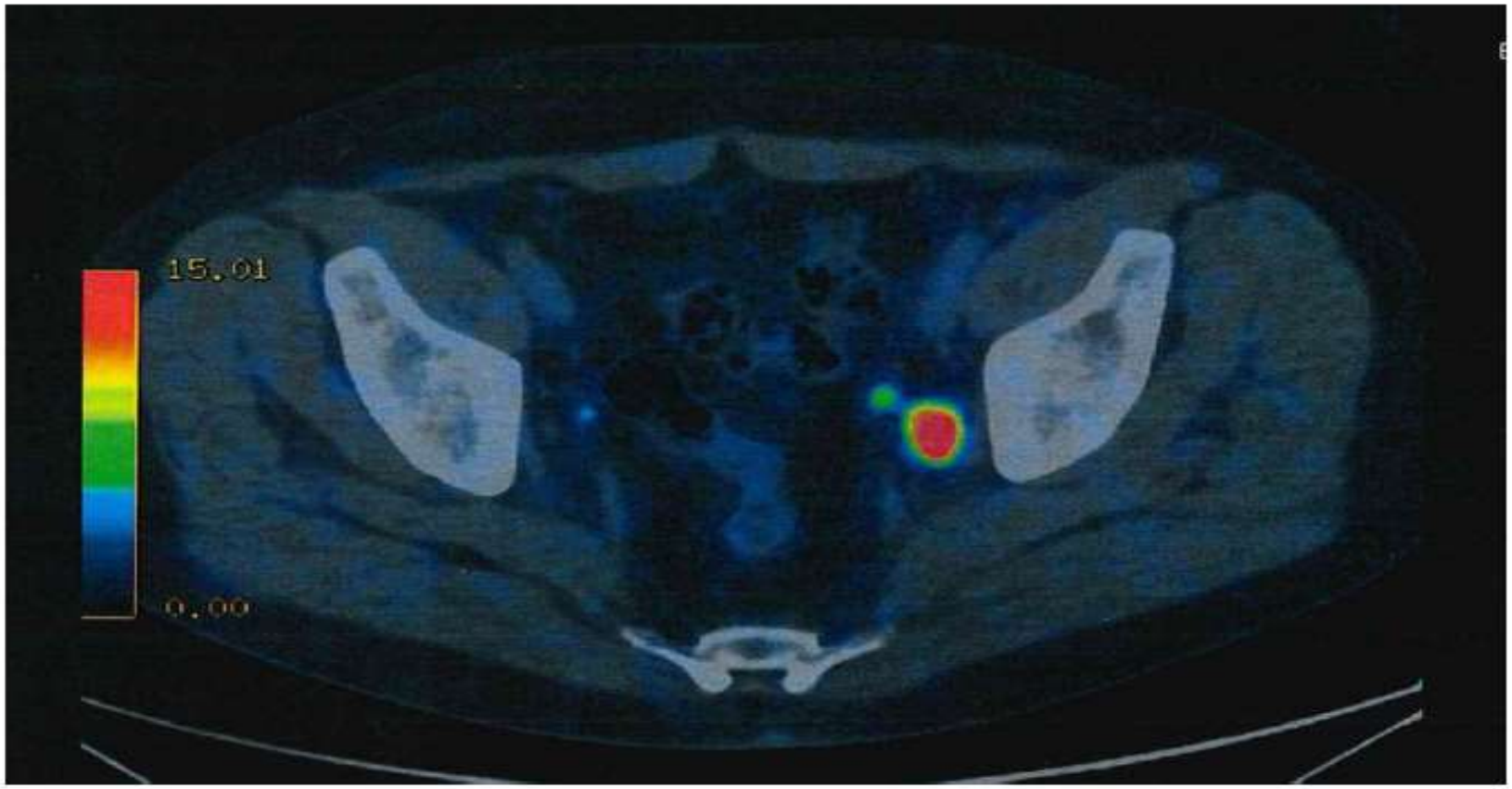


FIGURE 2 | ^{68}Ga-PSMA ligand PET/CT exhibits solitary left iliac radiotracer-positive lymph node.

Helen Diller Family Comprehensive Cancer Center

Theranostics

- The use of a compound for both diagnostics and therapeutics

This end of the molecule can be linked to an imaging radioisotope (Ga-68) or a therapeutic radioisotope (Lu-177)

This end of the molecule binds to the target (PSMA)

Slide courtesy of Tom Hope

Schottelius 2015 EJNNMI

Conclusions

- In a malignancy where immune checkpoint monotherapy has shown limited activity, NIVO+IPI demonstrated antitumor activity in patients with mCRPC
  - Benefit was observed regardless of prior exposure to chemotherapy, but appeared to be more pronounced in patients not receiving prior chemotherapy for mCRPC
  - Deep and durable objective responses, as well as PSA <0.2 ng/mL, were observed in a subgroup of patients
- Preliminary data suggest that biomarkers may have a role in identifying patients with mCRPC likely to respond to immunotherapy
  - Patients with PD-L1 ≥1% and/or HRD+ or DDR+ tumors achieved numerically higher objective response rates, although there was a small number of patients in the analysis
- Despite TMB being relatively low in prostate cancer versus other tumor types (melanoma, NSCLC), a significant association was observed between higher TMB and improved outcomes in this population
- The safety profile of NIVO+IPI was generally consistent with prior studies of the NIVO1+IPI3 dosing schedule; however, dose/schedule optimization will be important for patients with mCRPC given the number of patients not completing all 4 combination doses and discontinuing study treatment due to toxicity
- Further study of NIVO+IPI in patients with mCRPC is warranted

Conclusions

- The optimal sequence of agents is yet to be determined
- Abiraterone+prednisone, enzalutamide, apalutamide, daralutamide and docetaxel improve survival in hormone sensitive prostate
- Immune therapy should be given early in asymptomatic non visceral patients
- All CRPC patients should be tested for MSI.
- PARP inhibition is a promising therapeutic target in patients with BRCA mutations