Targeted Therapy in Prostate Cancer

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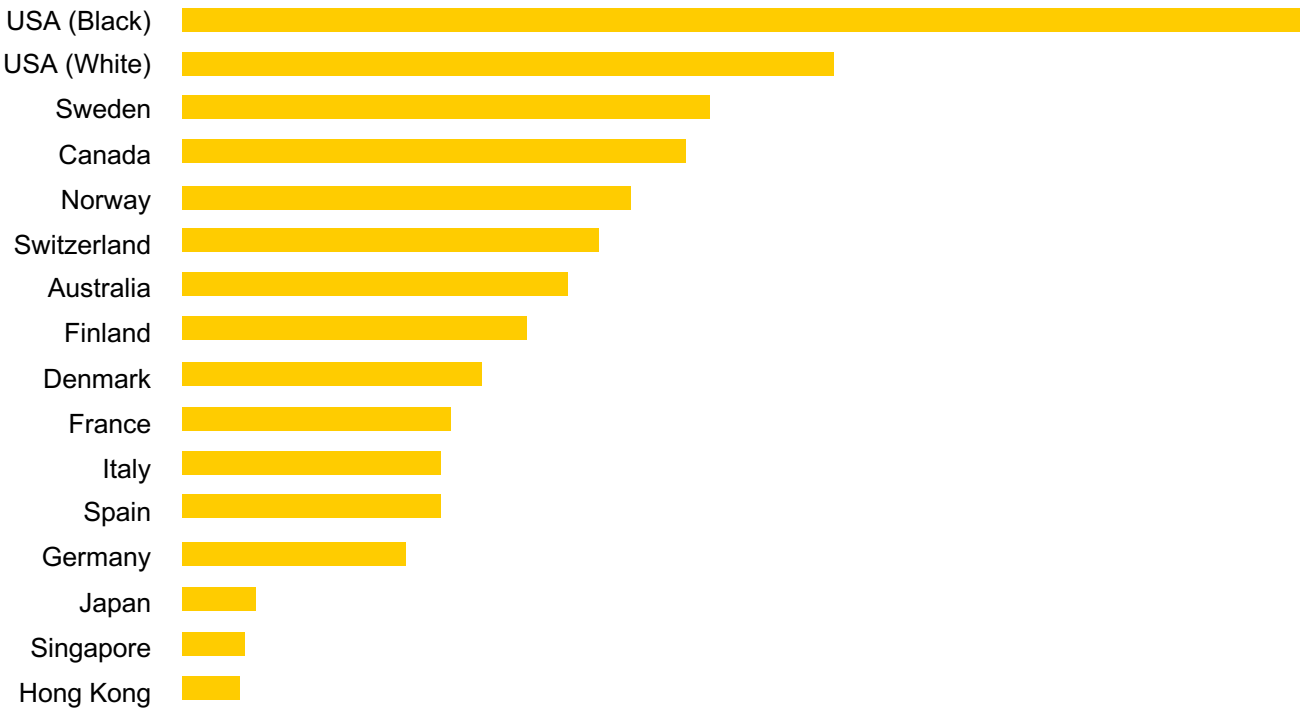
Prostate Cancer (Epidemiology)

- Over approximately 900,000 cases world-wide
  - Over 250,000 deaths world-wide (28%)

- U.S. approximately 241,000 cases
  - Over 30,000 deaths (12%)

Epidemiology

- Worldwide incidence and mortality vary significantly
- Histologic prevalence is essentially similar
  - 30-50% of men over have PC at autopsy



Epidemiology

Worldwide incidence and mortality vary significantly

- Highest clinical incidence in African Americans
- High clinical incidence Western countries
- Low clinical incidence in Far East

Histologic prevalence similar worldwide

- 30%-50% men have prostate cancer at autopsy

Initiation of disease common

Promotion to clinical disease varies

Characteristics of PC

- Chromosomal deletions (LOH) universal feature of human cancer

- Unlike other solid tumors (e.g., RCC, CRC, breast cancer) PC shows inconsistent chromosomal deletions

    - There is extensive genetic heterogeneity

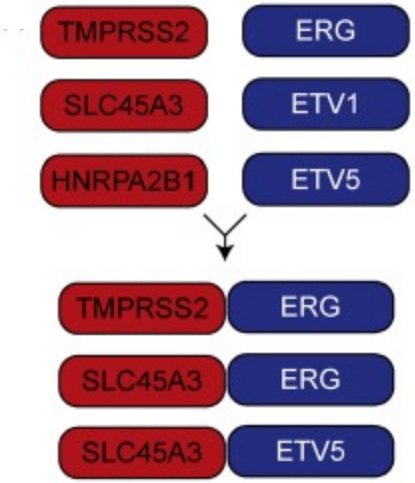
- Hereditary PC (HPC) linkage analysis has shown several susceptibility loci

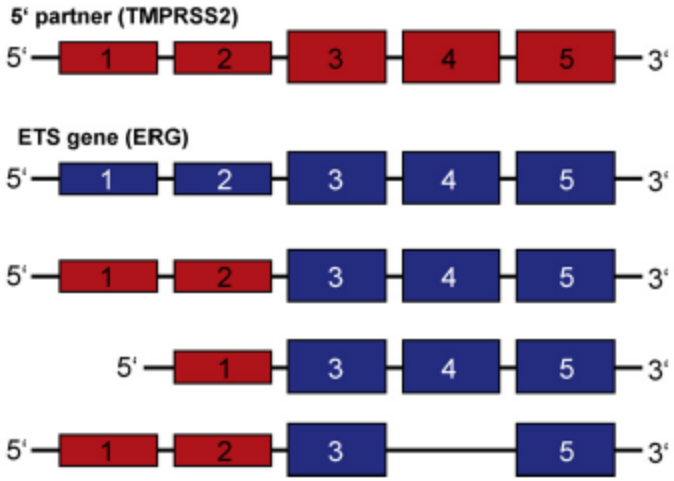
    - There is extensive genetic heterogeneity in HPC

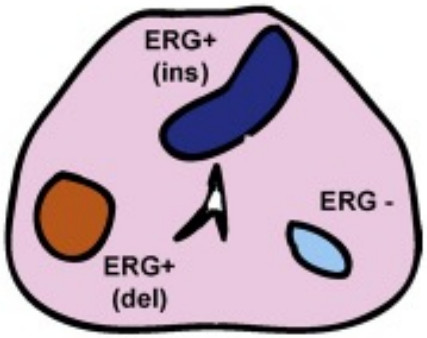
Characteristics of PC

- **Marked morphologic/ histologic heterogeneity**
  - Multifocal
  - > 1 histologic grade
  - Often admixed with benign pathology

- **Non-palpable PC in RP specimens**
  - Up to 45% of high-grade tumor (grade 4, 5) < 1cm3
  - aggressive disease can occur early in small tumor







ETS gene fusions in prostate cancer

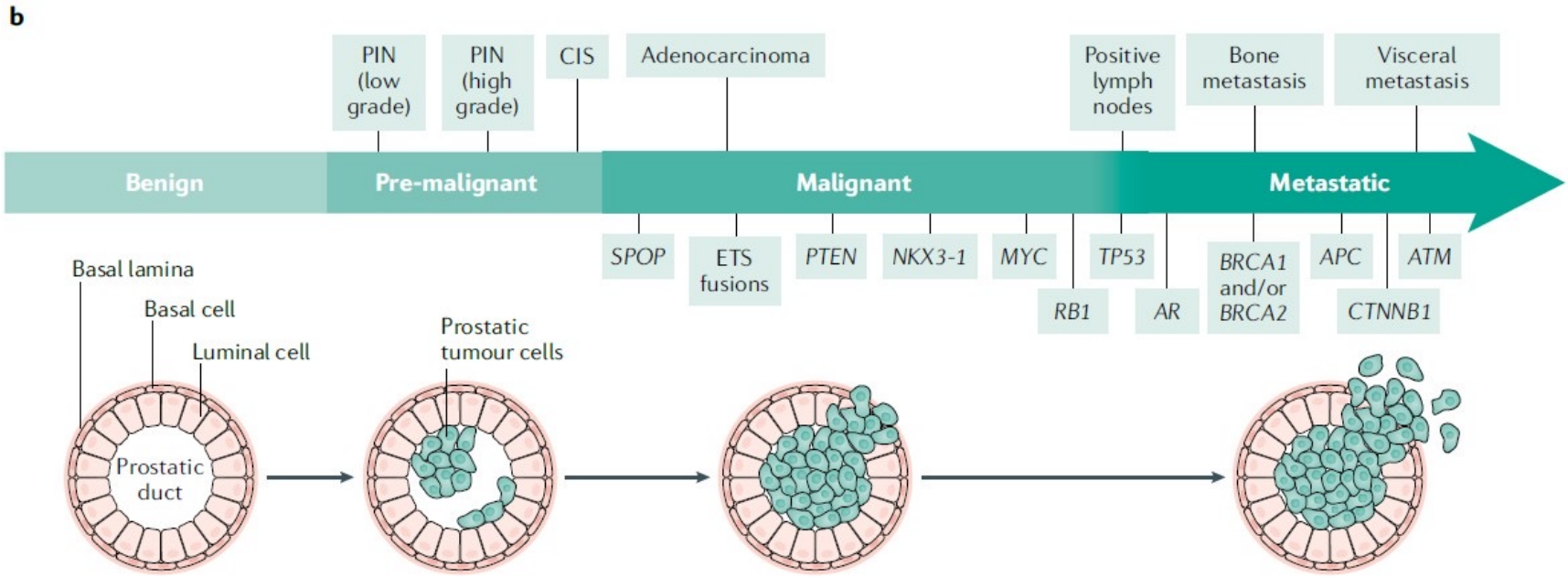
Tomlins et. al.

EUROPEAN UROLOGY 56 (2009) 275–286

Oncogenesis/TSG

- **Oncogenes**
  - **- Expression level**
    - Ras, myc, sis, fos, EGFR, c- erbB2: found in varying frequencies
    - Bcl2: in two-thirds of CRPC
  - **- Increased gene copy number**
    - C-myc: 11%, cyclin D1: 5%
- **Tumor Suppressor Genes**
  - **- p53**
    - Most consistently mutated (advanced disease)
    - Heterogeneity of p53 mutations within different tumors in same gland
  - **- Others:** PTEN, Rb, p16, p27, E-cadherin
  - **- Aggressive Variant Prostate Cancer (AVPC):** ***PTEN, p53, Rb***

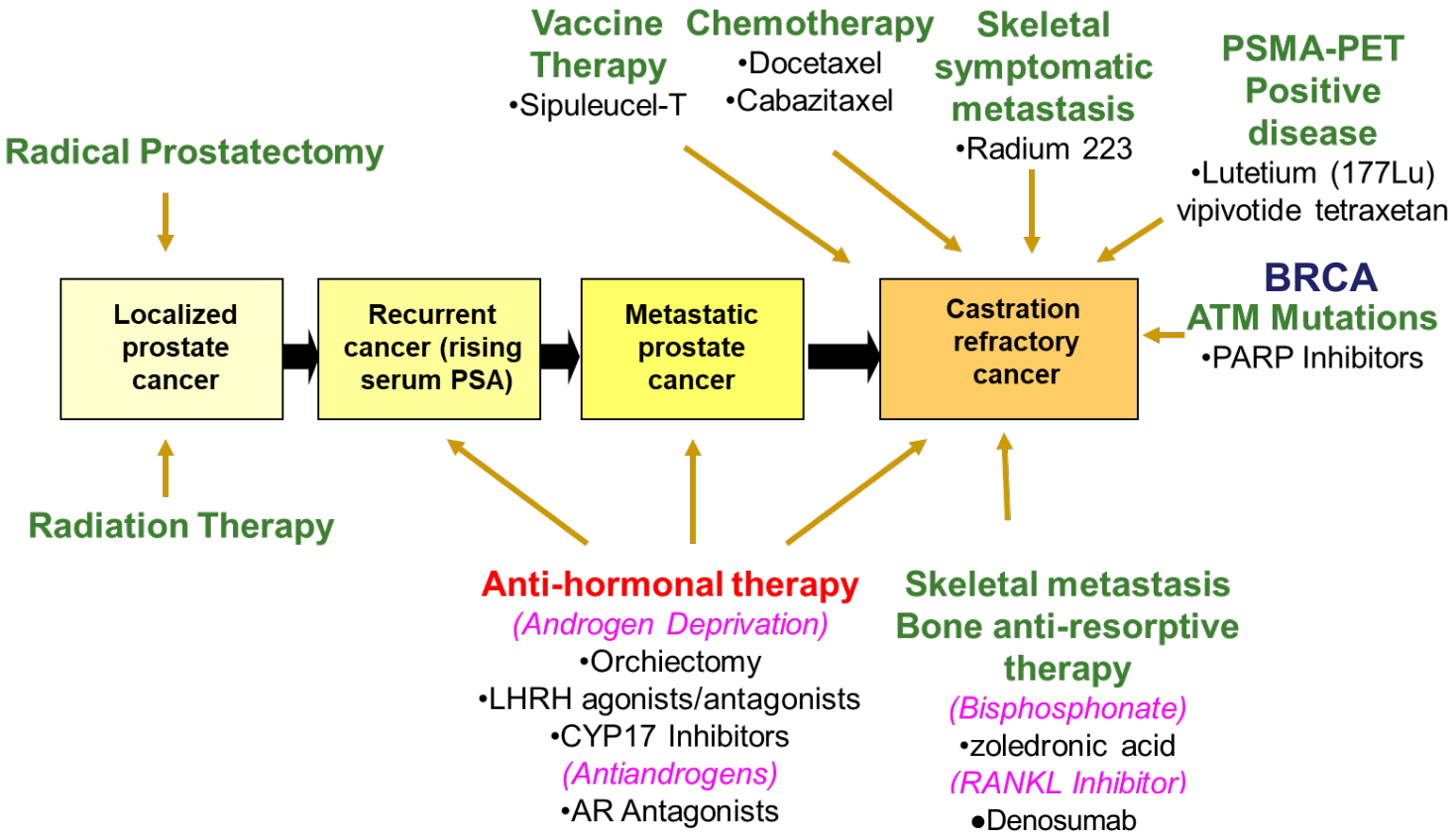
Pathogenesis: histologic transformation



Mills et al, 2014.

Clinical Presentation of PC

- Clinically Localized ~75%
- LAPC ~10 – 15%
- Metastatic <5 - 10%



Prostate cancer progression and treatment

Role of Androgen/AR in Prostate Cancer

- **Androgens under normal conditions cause differentiation**

- **In Prostate Cancer why are androgens proliferative?**

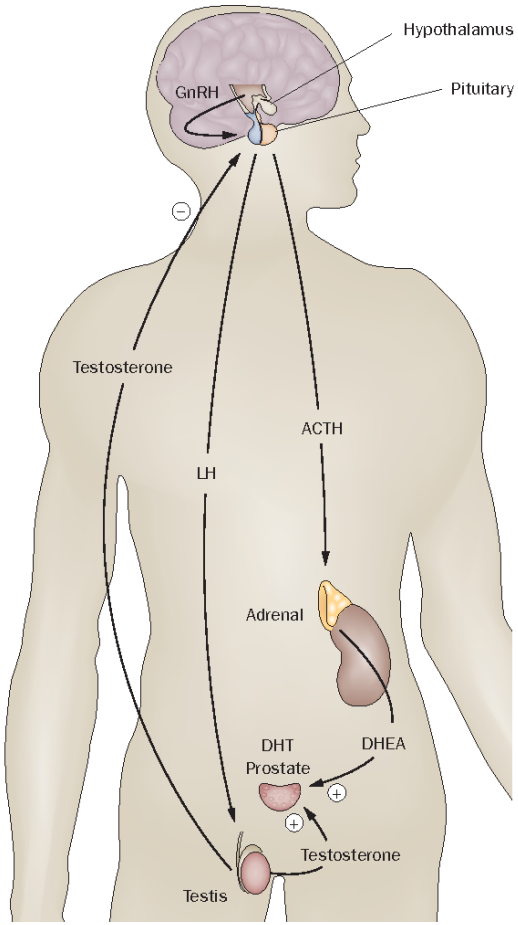
  - TMPRSS2-ETS translocation as one possible explanation

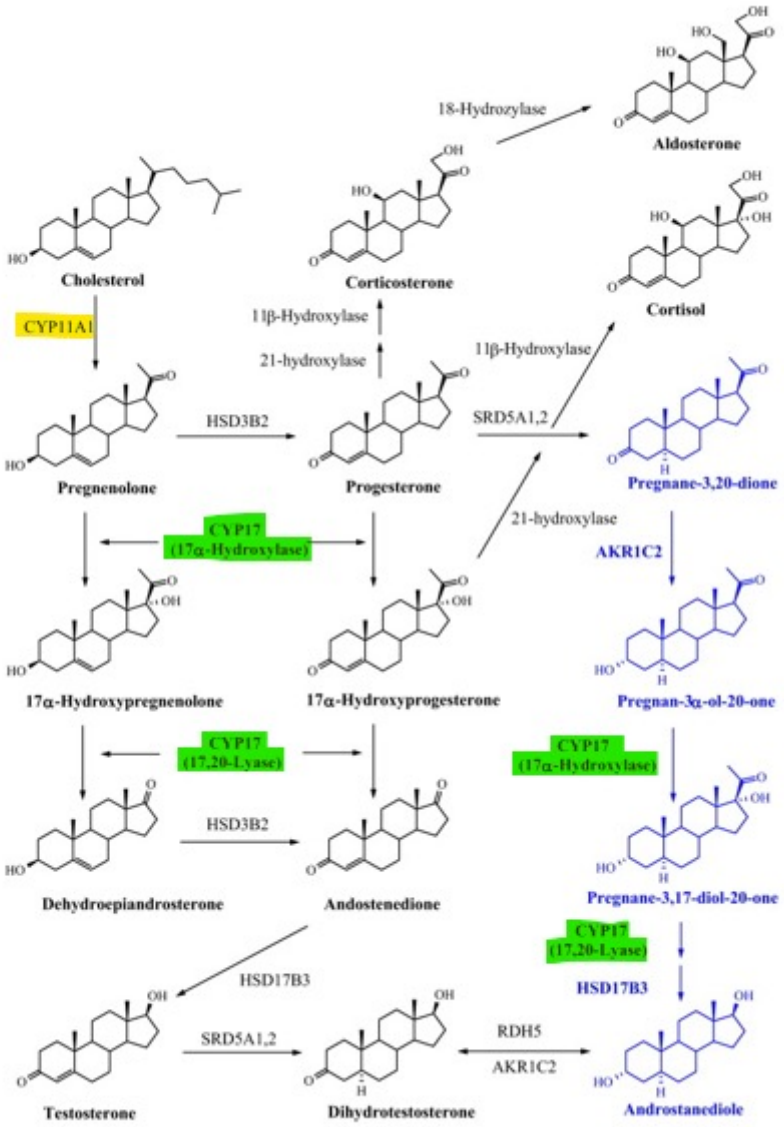
- **Role of Androgen Deprivation Therapy *('hormone therapy')* in Prostate Cancer**

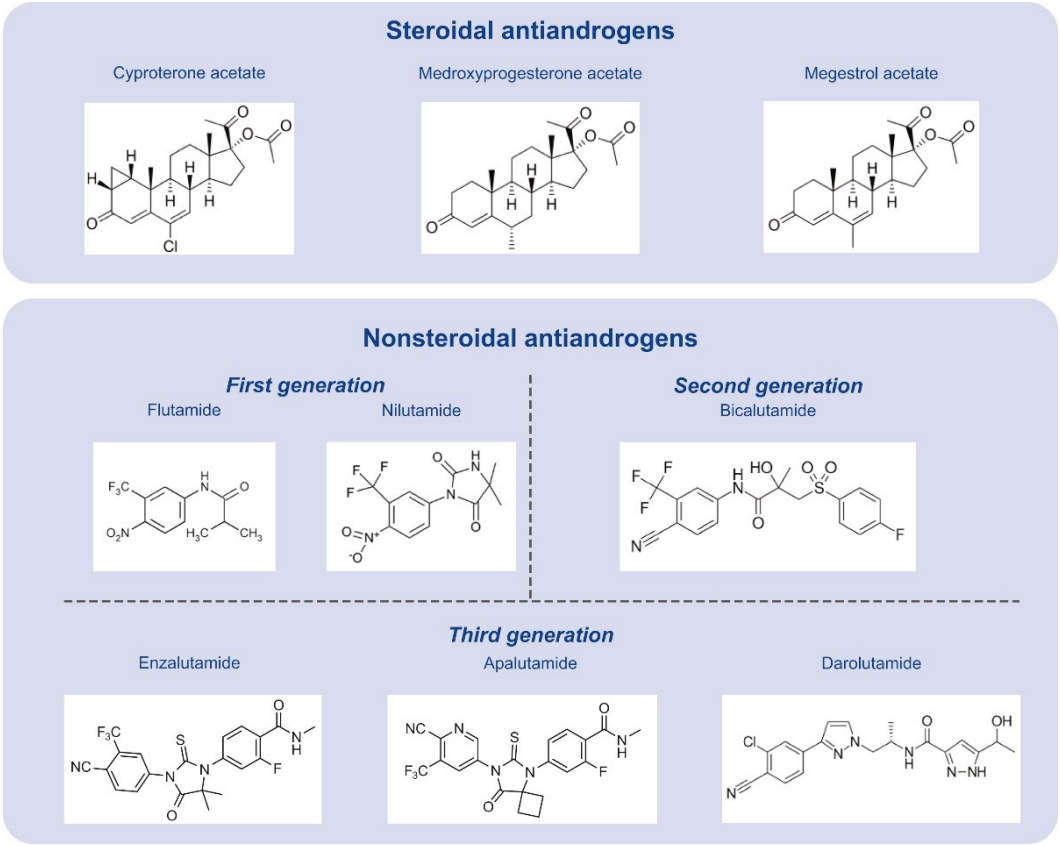
  - 80% of patients respond initially, PSA decreases

- **ADT invariably fails: PSA increases in spite of castrate levels of testosterone**

  - Castrate Resistant Prostate Cancer (CRPC)
  - Gain of Function in AR

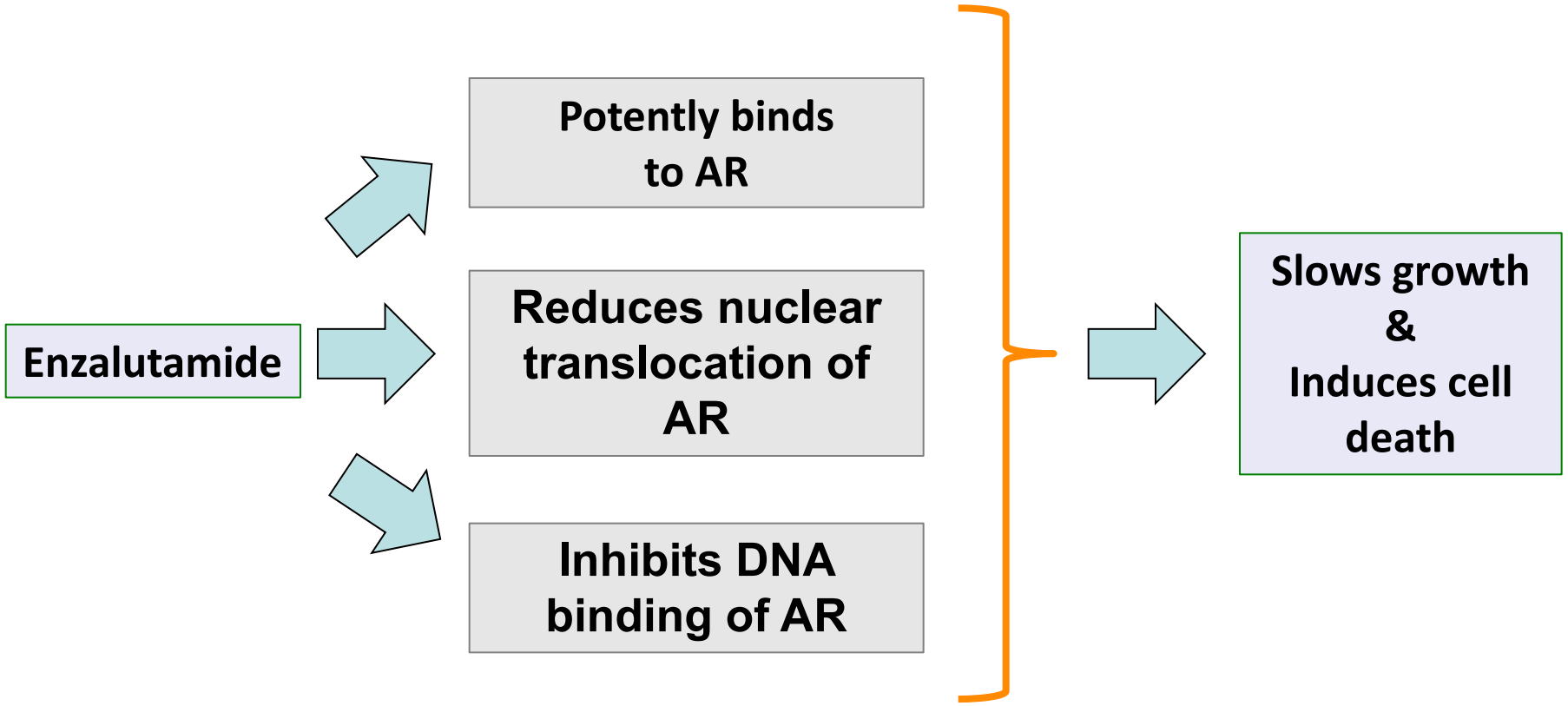

Hypothalamus
Pituitary
GnRH
Testosterone
LH
ACTH
Adrenal
DHT
Prostate
DHEA
Testosterone
Testis


Cholesterol
CYP11A1
Pregnenolone
HSD3B2
Progesterone
17α-Hydroxypregnenolone
CYP17 (17α-Hydroxylase)
17α-Hydroxyprogesterone
Dehydroepiandrosterone
CYP17 (17,20-Lyase)
HSD3B2
Andostenedione
Testosterone
HSD17B3
SRD5A1,2
Dihydrotestosterone
RDH5
AKR1C2
Androstanediole
21-hydroxylase
11β-Hydroxylase
Corticosterone
18-Hydrozylase
Aldosterone
Cortisol
11β-Hydroxylase
SRD5A1,2
Pregnane-3,20-dione
21-hydroxylase
AKR1C2
Pregnan-3α-ol-20-one
CYP17 (17α-Hydroxylase)
Pregnane-3,17-diol-20-one
CYP17 (17,20-Lyase)
HSD17B3



Chemical structure of steroidal and nonsteroidal antiandrogens

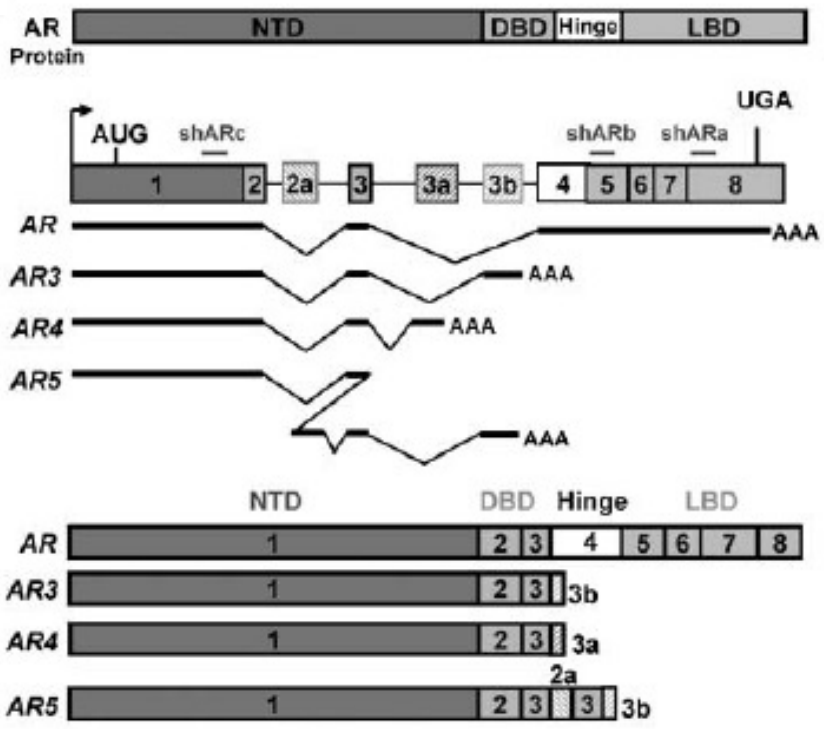
Enzalutamide: AR Antagonist



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

Gain of Function of Androgen Receptor

- Changes in coactivator/corepressor expression
- Ligand independent activation of AF (e.g. other growth factors/signaling pathways)
- Increase AR expression
- AR mutations that broaden specificity of ligand
- AR isoforms that may be ligand-independent
- Intra-tumoral synthesis of androgens
  - Exploit alternate pathway: **DHEA** → **AD** → **5α AD** → **DHT** that bypasses Testosterone synthesis
  - Gain of stability mutation in **3βHSD**, which converts **DHEA** → **AD** (Sharifi, Cell 2013)
- In CRPC glucocorticoid receptor (GR) may substitute for AR in some patients (Sawyers, Cell 2013)



AR variants

Guo et. al.

Cancer Res 2009; 69: (6). March 15, 2009

Metastatic Castration Sensitive Prostate Cancer

- **First line therapy is hormone ablation**
  - > 80% patients respond
  - Duration of response is ~18-24 months with GAS
  - Duration of response *increase by ~ 12 additional* months with GAS + AR axis targeting agents to GAS
- **Types of hormone treatments (next generation)**
  - Androgen Axis Targeting
    - Androgen biosynthesis inhibitors
      - Abiraterone
    - Non- Steroidal
      - Enzalutamide
      - Apalutamide
      - Darolutamide

Hormonal Therapies in Metastatic *Castration Sensitive* Prostate Cancer *(CSPC)*

- Gonadal androgen suppression (GAS): surgical/medical castration
- Combined androgen suppression (GAS + AR axis targeted agents = 'hormonal intensification')
- Androgen deprivation therapy (GAS) + docetaxel chemotherapy
- Combined androgen suppression (ADT + AR axis targeting) + docetaxel
  - PEACE-1 Trial (ADT + Abiraterone + Docetaxel)
  - ARASENS Trial (ADT + Darolutamide + Docetaxel)

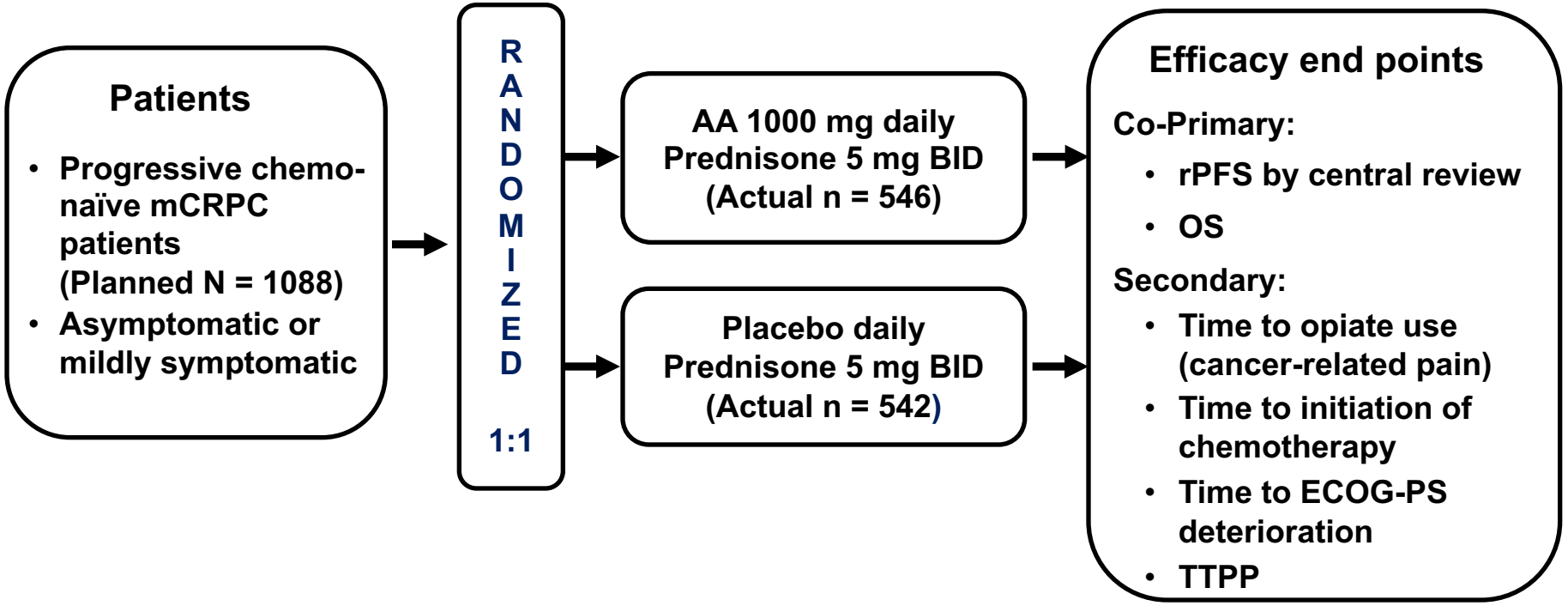
Hormonal Therapies in Metastatic Castration *Resistant* Prostate Cancer (CRPC)

- Patients then develop progressive disease despite castrate levels of serum testosterone, i.e. Castration Resistant Prostate Cancer (CRPC)

- In CRPC there is re-expression of Androgen Regulated Genes (ARG), i.e. there is recruitment of AR-dependent signaling
  - PSA starts rising despite 'castrate' levels of serum testosterone

- Therefore, in CRPC there is rationale to:
  - Further decrease androgen biosynthesis
  - Disrupt AR function

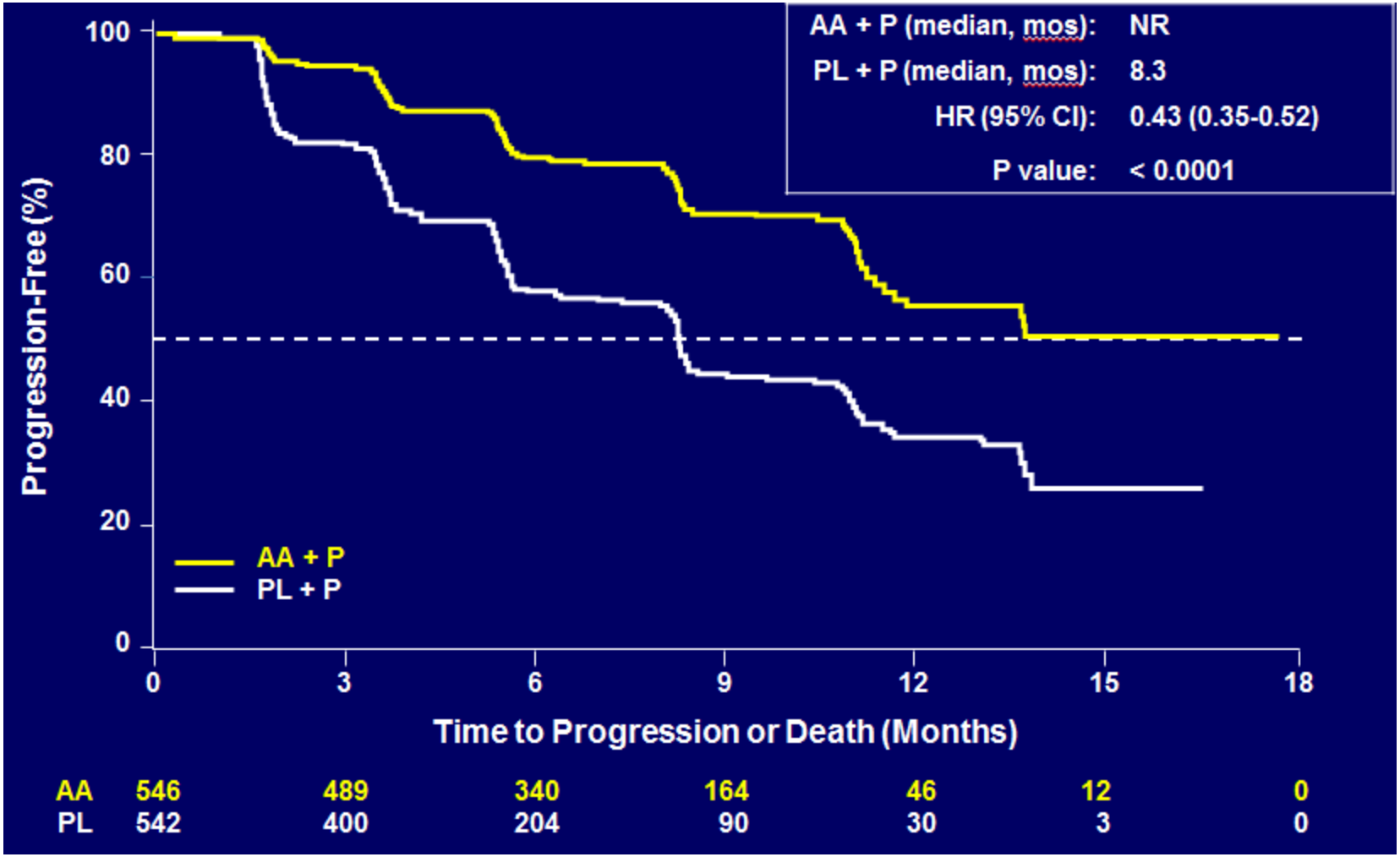
Abiraterone in Metastatic *CRPC* (*pre-docetaxel*) COU-302 Trial



- 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

Ryan CJ et al. Oral presentation ASCO, Chicago, 2 June 2012

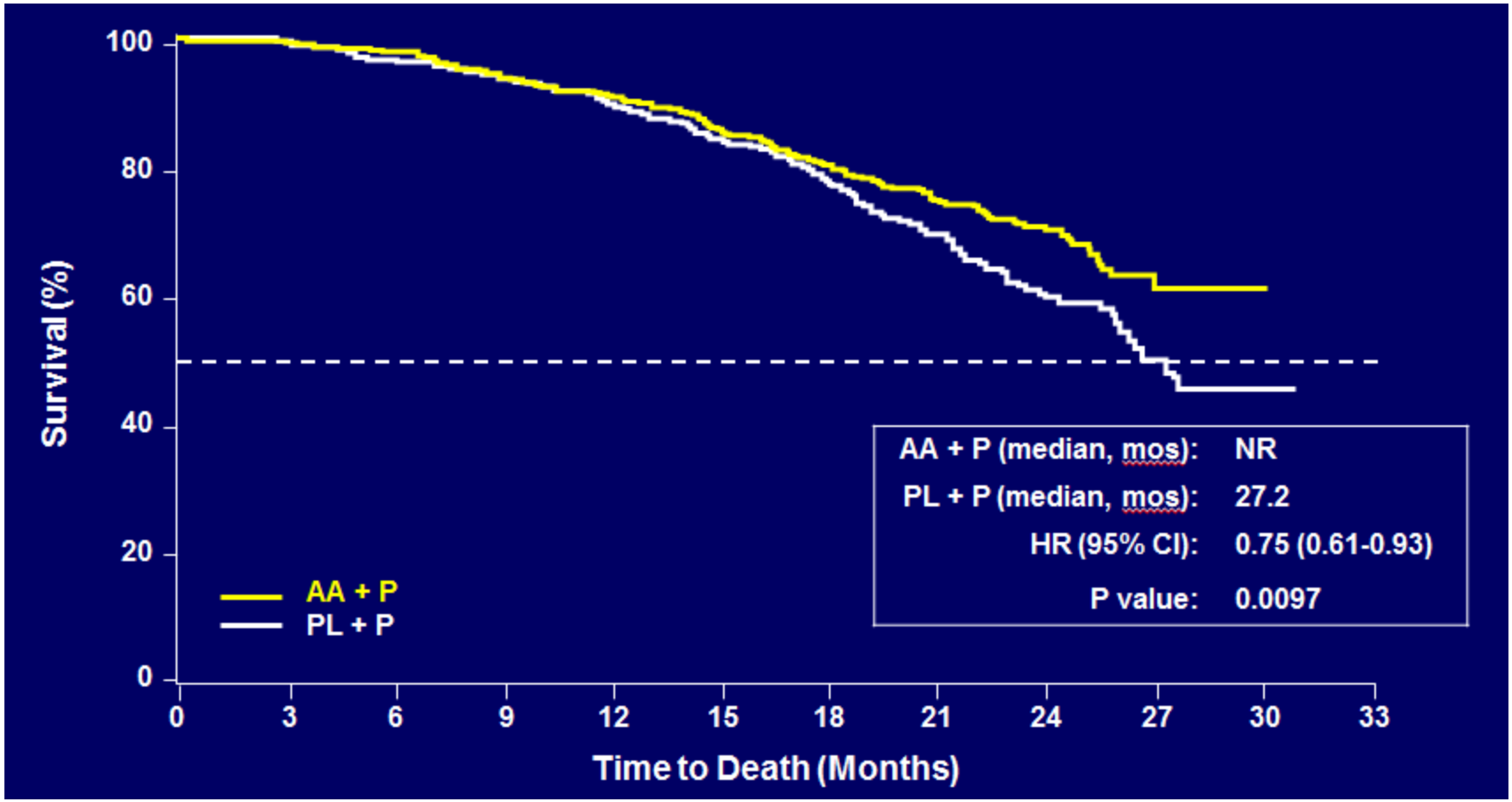
Statistically Significant Improvement in rPFS Primary End Point



Data cutoff 12/20/2010.
NR, not reached; PL, placebo.

Ryan CJ et al. Oral presentation ASCO, Chicago, 2 June 2012

Strong Trend in OS Primary End Point



AA	546	538	524	503	482	452	412	258	120	27	0	0
PL	542	534	509	493	465	437	387	237	106	25	2	0

Data cutoff 12/20/2011.

Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

Abiraterone in *mCRPC* (*post docetaxel*): COU 301 Trial

- **N = 1195 pts; 2:1 randomization; all pts previously received docetaxel**

- **AA 1000 mg/day + Pred 10 mg/day vs. Placebo + Pred 10 mg/day**
  - Median follow up 13 months

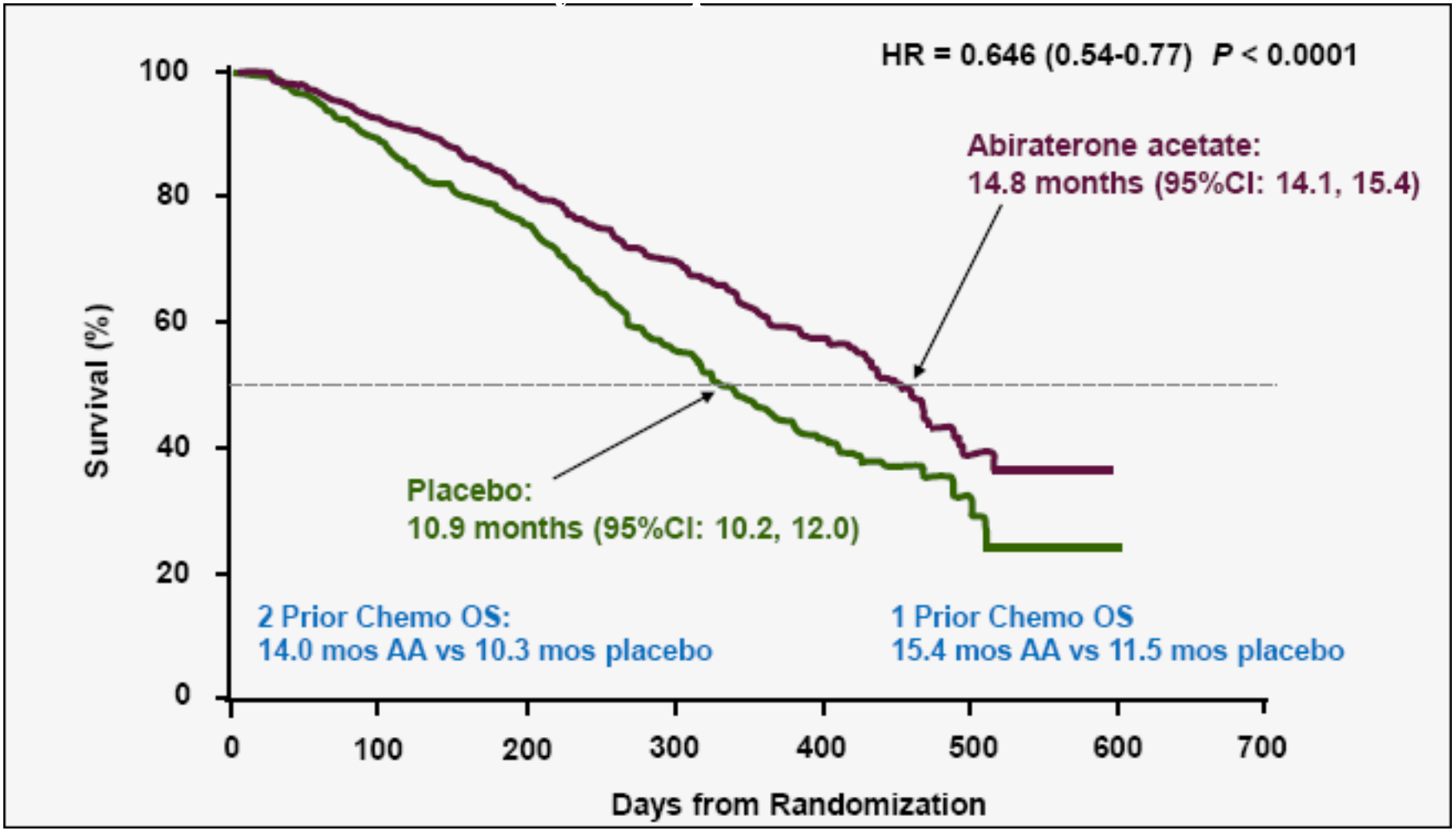
    OS: 14.8 months vs. 10.9 months (HR 0.65)

    PFS: 5.6 months vs. 3.6 months

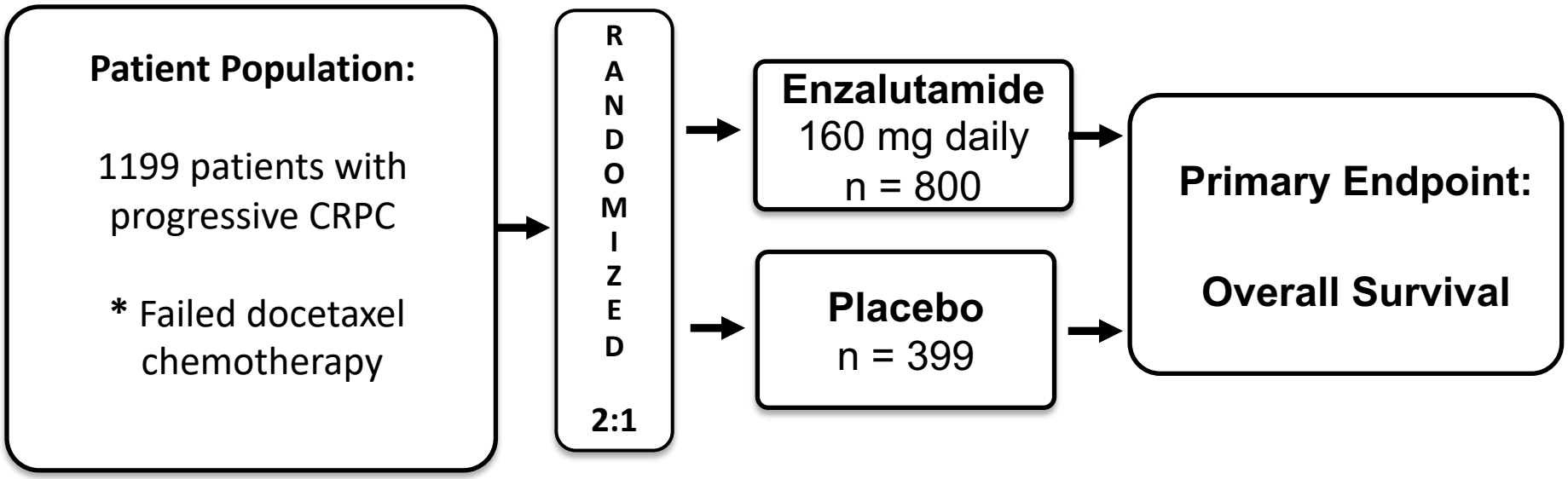
    PSA response: 29% vs. 6 %

- **Secondary analysis**
  - 90% pts had bone metastasis, 44% had significant pain
  - Statistically significant improvement in pain, time to first SRE

Abiraterone in Metastatic *CRPC* (*post docetaxel*)
COU-301 Trial



AFFIRM: A Phase III Trial of Enzalutamide vs. Placebo in *Post-Chemotherapy* Treated mCRPC

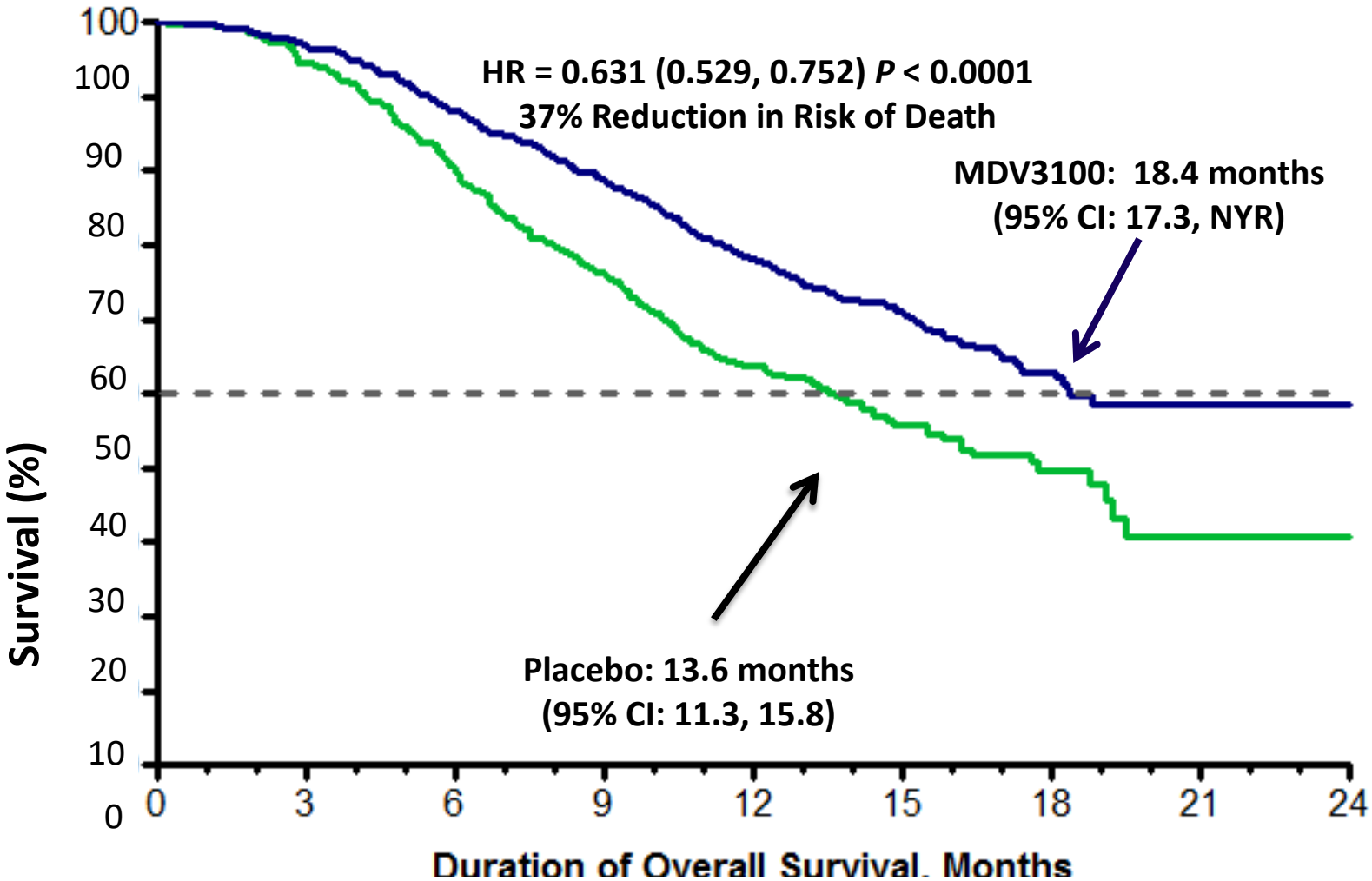


Co- Principal Investigators:
H. Scher & J. De Bono

Clinicaltrials.gov identifier:
NCT00974311

* Glucocorticoids were not required but allowed

Enzalutamide Prolongs Survival by a Median of 4.8 Months



De Bono J. Presented at the 2012 ASCO Annual Meeting. Chicago, IL

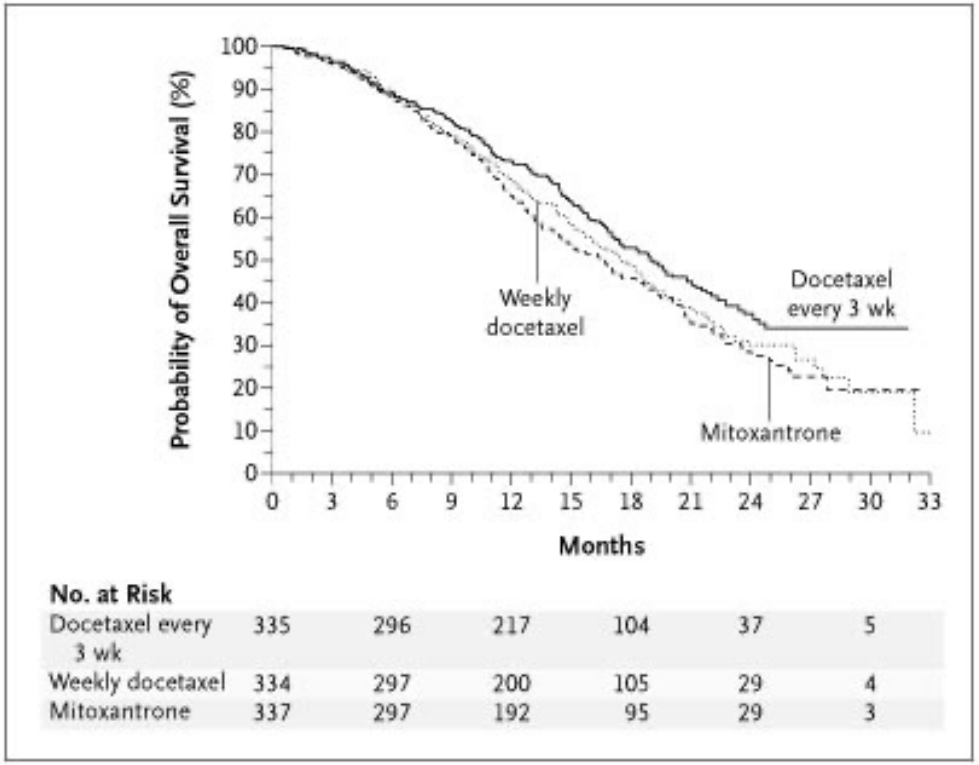
Hormonal Therapies in Metastatic Prostate Cancer

- Metastatic Castration *Resistant* Prostate Cancer
  - ADT + Abiraterone: COU-301 (post docetaxel), COU-302 (pre-docetaxel)
  - ADT + Enzalutamide: AFFIRM (post docetaxel), PREVAIL (pre-docetaxel)
- Metastatic Castration *Sensitive* Prostate Cancer
  - ADT + Abiraterone: LATTITUDE, STAMPEDE
  - ADT + Enzalutamide: ENZAMET, ARCHES
  - ADT + Apalutamide: TITAN

Chemotherapy

- Low dose po Cytoxan
- 5 FU
- Doxorubicin
- Doxorubicin + 5FU
- Doxorubicin + Stilphostrol
- Doxorubicin + Ketoconazole
- Vinblastine
- Vinorelbine
- Estramustine (EMP)
- EMP+Vinblastine
- EMP + Etoposide
- EMP+Taxanes
- Epothilones
- Satraplatin
- Mitoxantrone
- Docetaxel
- Cabazitaxel

TAX 327: Overall Survival (mCRPC)



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

	Median (mos)	Hazard survival	*P-value* ratio*
-D Q3 weeks:	18.9	0.76	0.009
-Mitoxantrone	16.5	--	--

*Compared to mitoxantrone

NOTE: In the weekly (docetaxel) injection concentrate arm, no overall survival advantage was demonstrated compared to the mitoxantrone control..

Phase III Trials of Docetaxel Combinations

Doc/Pred vs Doc/ Combined With:	Status	Results
DN-101	Terminated early	Negative
GVAX	Terminated early	Negative
Bevacizumab	Completed	Negative
VEGF-Trap	Completed	Negative
Atrasentan	Completed	Negative
ZD4054	Completed	Negative
Dasatinib	Completed	Negative
Lenalidomide	Completed	Negative
Custersin (OGX-011)	Completed	Negative

To date, no combination improves on docetaxel and pred

Cabazitaxel (TROPIC Phase III Trial; mCPRC)

- N = 775 pts; *all received prior docetaxel*
- Cabazitaxel/Prednisone vs. Mitoxantrone/Prednisone
- Overall Survival favored cabazitaxel

  Median survival : 15.1 months vs. 12.7 months (HR 0.70)
  PFS : 2.8 months vs. 1.4 months (HR 0.74)
  PSA response : 39% vs. 18%

- Survival benefit greater for pts receiving more prior docetaxel (HR 0.51 for doc >900m/m2 vs. 0.96 for doc < 225 mg/m2)

Cabazitaxel in mCRPC

Proselica Trial (n=1200, mCRPC post Docetaxel)

Cabazitaxel 20mg/m2 vs. Cabazitaxel 25mg/m2

- median OS: 13.4 mo vs. 14.5 mo
- Grade 3/4 infections: 10% vs. 20%
- Neutropenic fevers: 2% vs. 10%

Firstana Trial (n=1168, chemotherapy-naive, 1:1:1)

Cabazitaxel 20mg/m2 vs. Cabazitaxel 25mg/m2 vs. Docetaxel 75mg/m2

- median OS: 24.5 mo vs. 25.2 mo vs. 24.3 mo
- Grade 3/4 toxicity: 41% vs. 60% vs. 46%

Chemo-hormone Therapy in Metastatic Castration Sensitive Prostate Cancer

- ADT + Chemotherapy (Docetaxel) – “Doublets”
  - CHAARTED
  - STAMPEDE
  - GETUG-AFU15
- ADT + AR Targeting + Chemotherapy (Docetaxel) – “Triplets”
  - PEACE-1: ADT + Abiraterone +/- Chemotherapy
  - ARASENS: ADT + Chemotherapy +/- Darolutamide

Immune Therapy in Prostate Cancer

Vaccines: *Generate anti-tumor response to specific tumor antigens*

Sipuleucel-T (PAP-GSF fusion protein used to prime autologous dendritic cells ex vivo and then reinfuse in pts to stimulate T cells)

Prostvac (PSA-triad of costimulatory molecules in viral vector given s.c. to prime dendritic cells in vivo which then stimuateT cells)

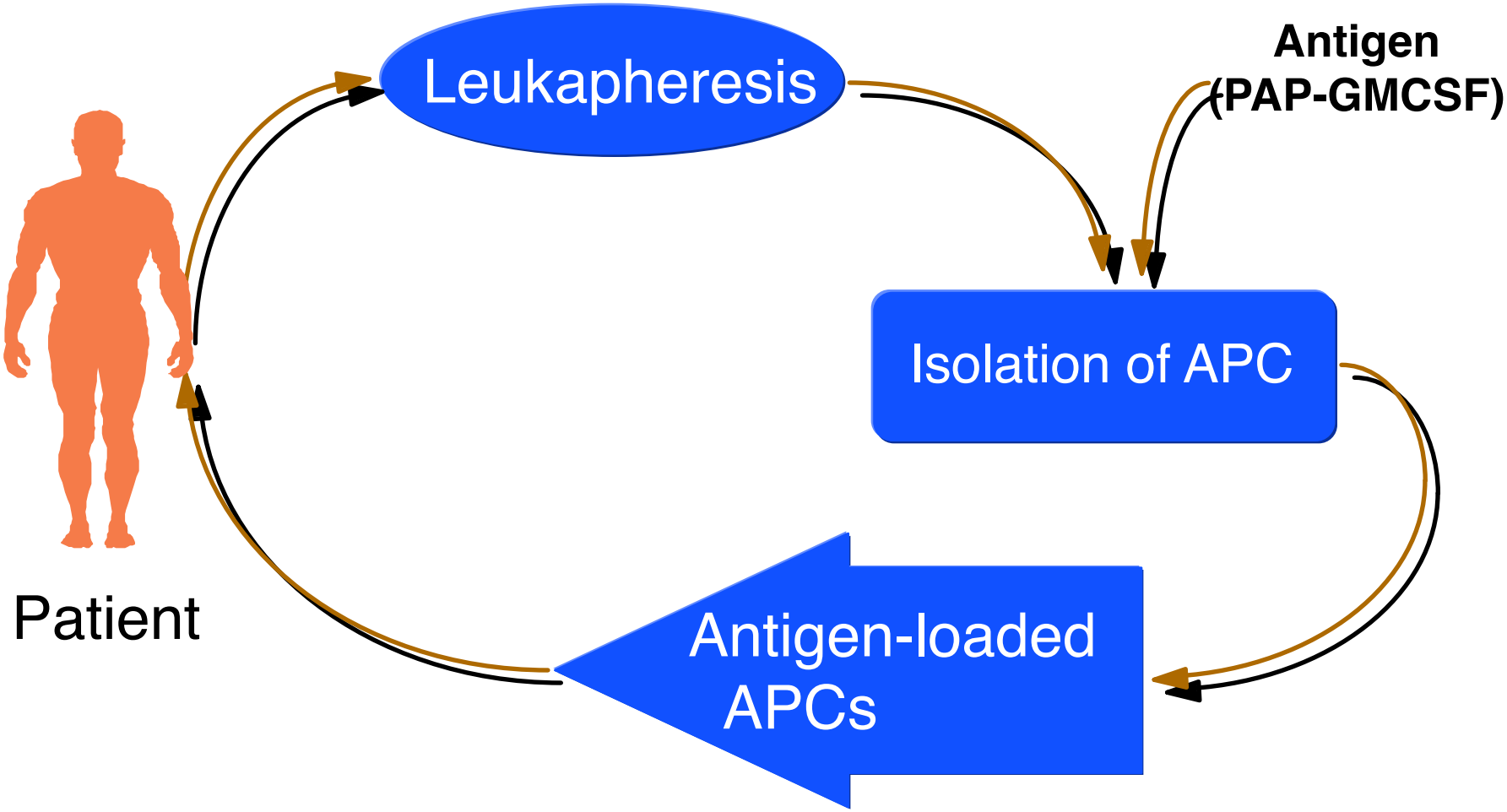
Immune Checkpoint Inhibitors: *Non-specific stimulation of T cells*

PD-1 (activated T and B cells)

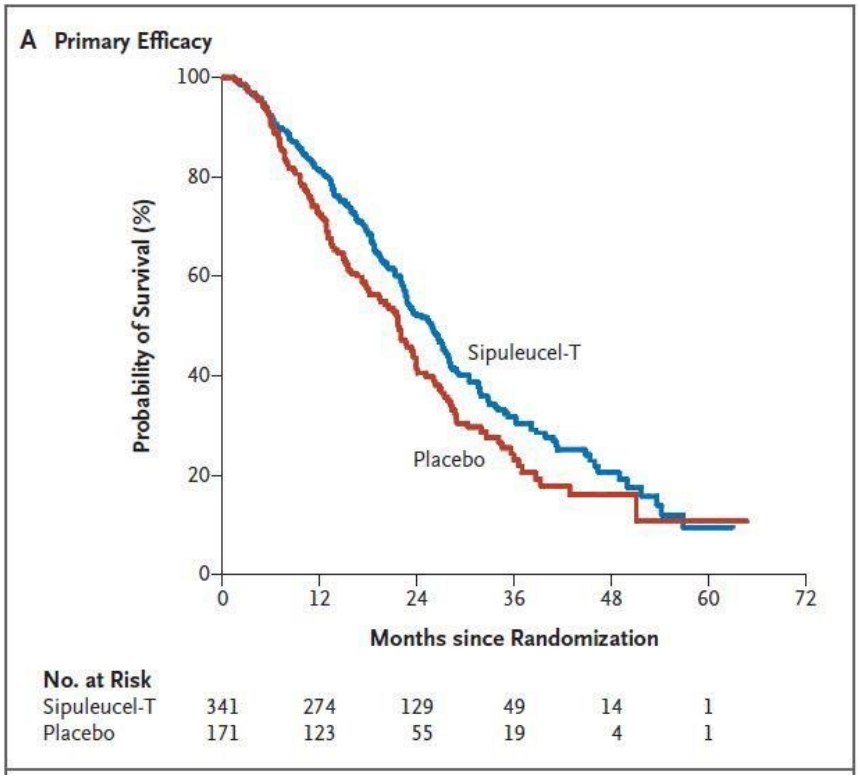
PD-L1 (expressed on tumor cells)

CTLA-4 (activated T cells)

Sipuleucel-T



m1CRPC: Sipuleucel-T: ↔PFS, ↑OS



512 patients
OS (25.8 vs. 21.7 mo)
HR for death (0.78; 95% CI 0.61 to 0.98; P=0.03)
Gr ≥3 AE: 31.7% vs 35.1%; chills, fever, headache

- **IMPACT 2010**
- Phase 3 randomized
- PSA ≥ 5, no visceral mets but bone mets OK, ±chemo
- IV infusions, q2weekly x 3
- Sipuleucel-T vs placebo

Kantoff PW, et al. NEJM 2010

Conclusions

- Immunotherapy may slow the growth rate of tumors and improve OS (but may not impact short term PFS)
- Immunotherapy may have delayed effect and for a longer period of time (in part may be due to antigen spreading)
- Earlier use of immunotherapy with less tumor burden is likely to be better

Radioisotopes: 50 years of progress

Sr-89:
Beta emmitter

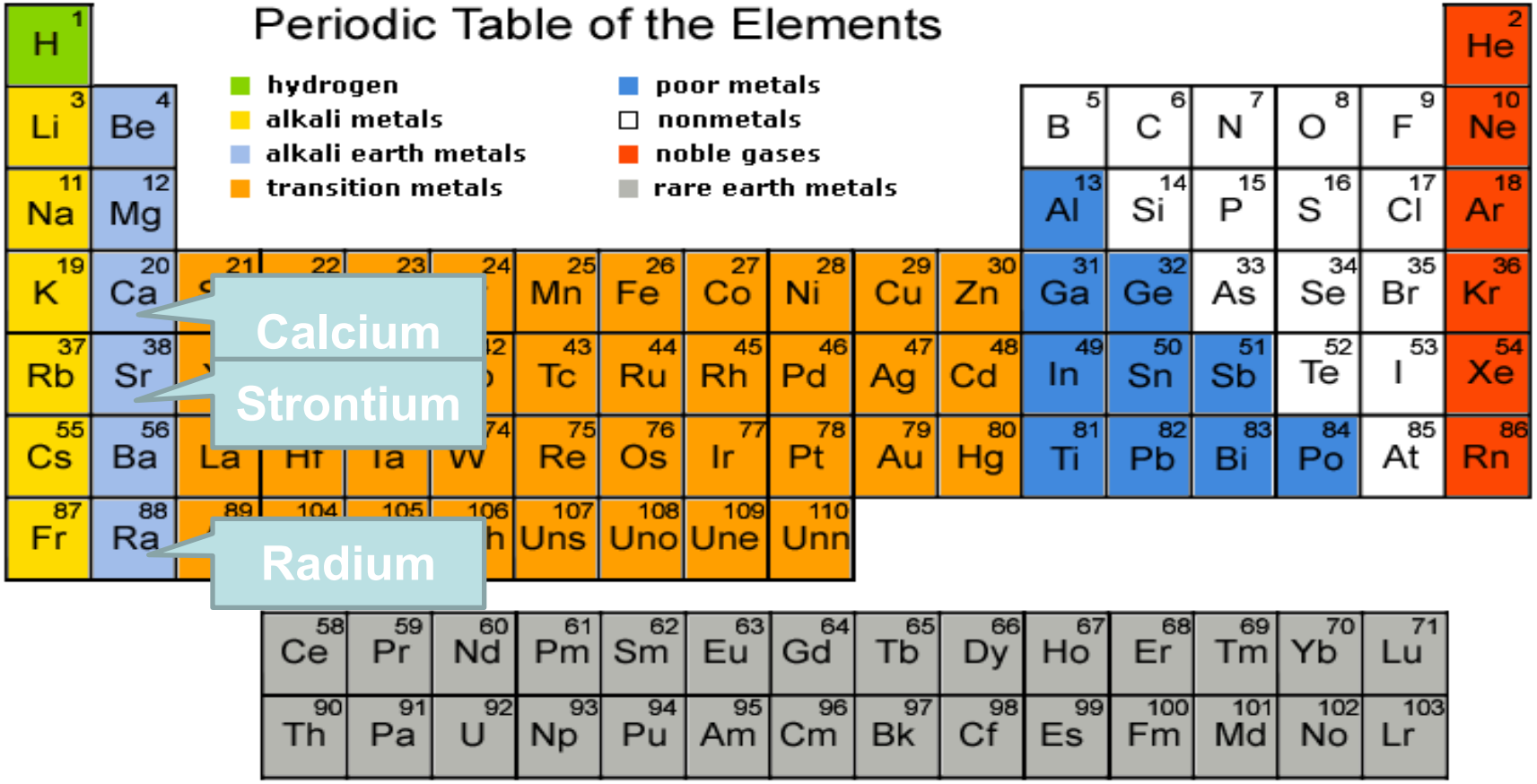
Disease palliation

Roy Larsen

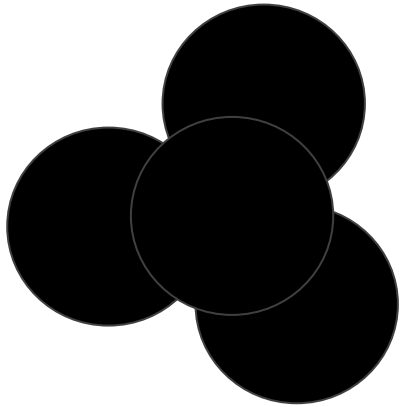
Ra-223:
Alpha emmitter

Overall survival

Radium and Strontium act as Calcium Mimetic Agents



α (Ra decay) and β (Sr decay) Particles

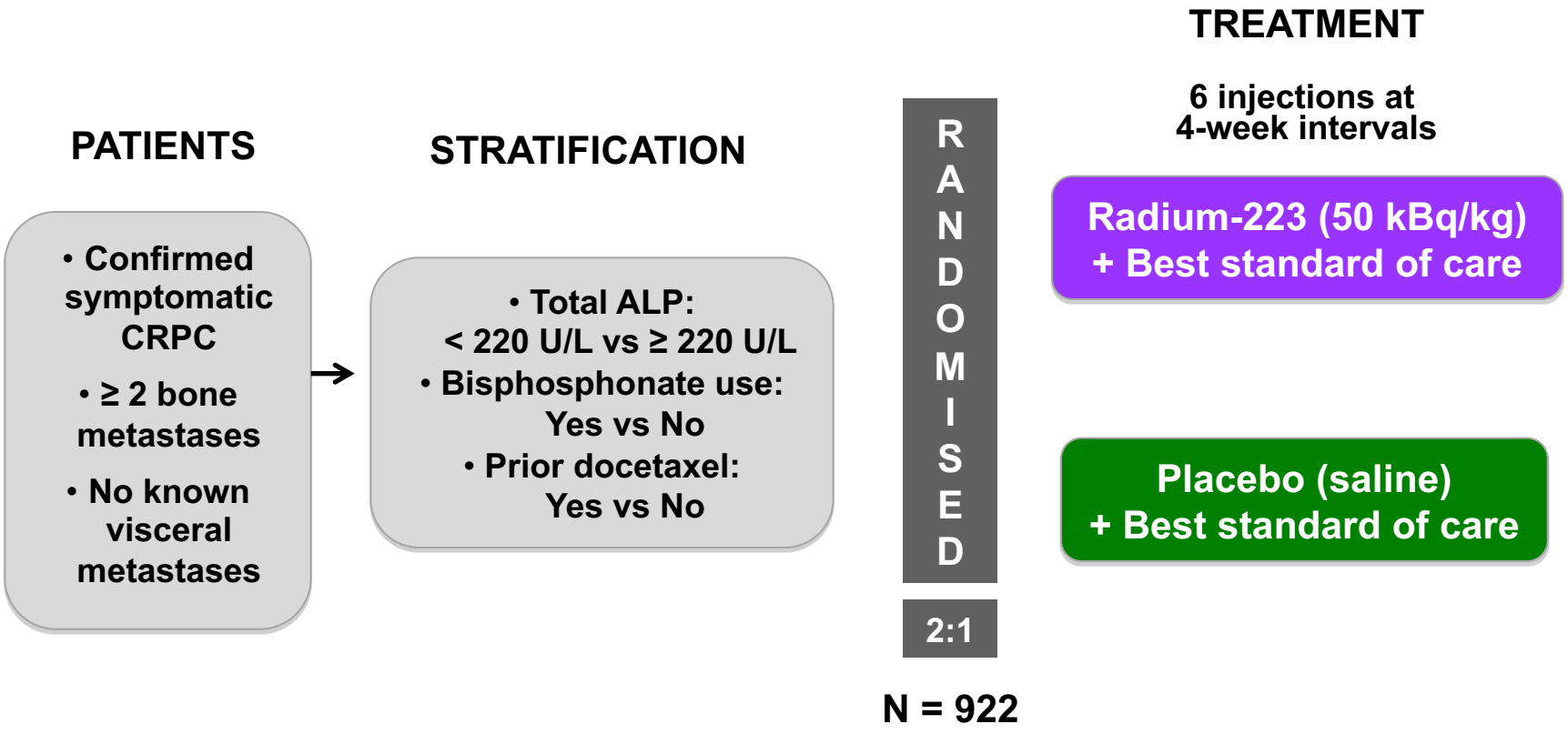


Alpha

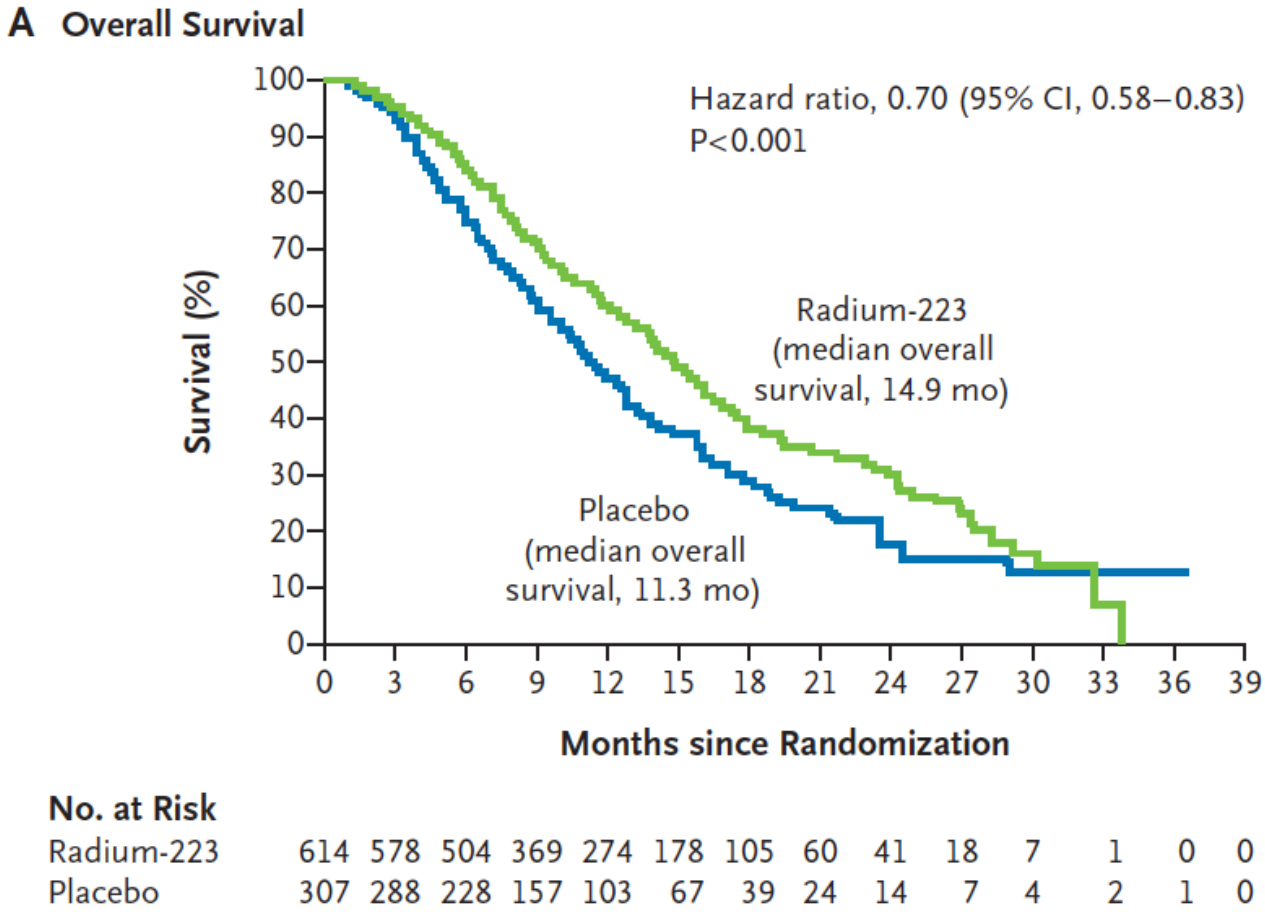
Beta

	α	β
Relative mass	7300	1
Range in tissue	0.1mm	5mm
Hits to kill a cell	1–10	100–1000

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



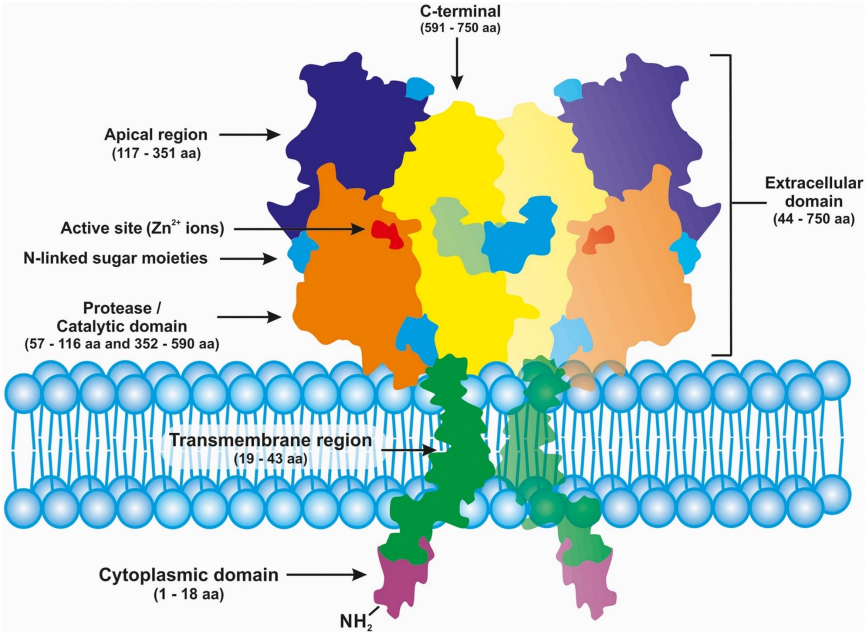
ALSYMPCA Overall Survival



Parker et al. NEJM (2013)

Prostate-specific membrane antigen (PSMA): molecular target for imaging and therapy in prostate cancer

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - E.g. salivary and lacrimal glands
- Excellent target for PET imaging



From Evans JC *et al. Br J Pharmacol* 2016;173:3041–3079

Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

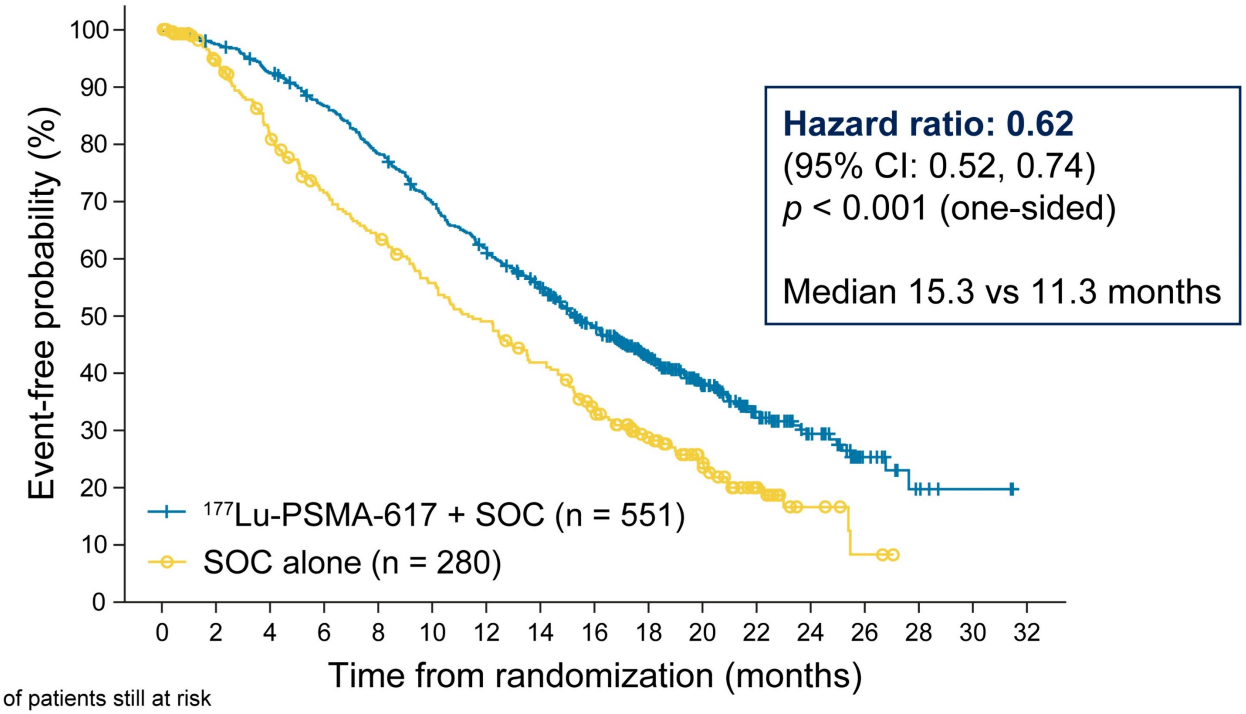
- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11

- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



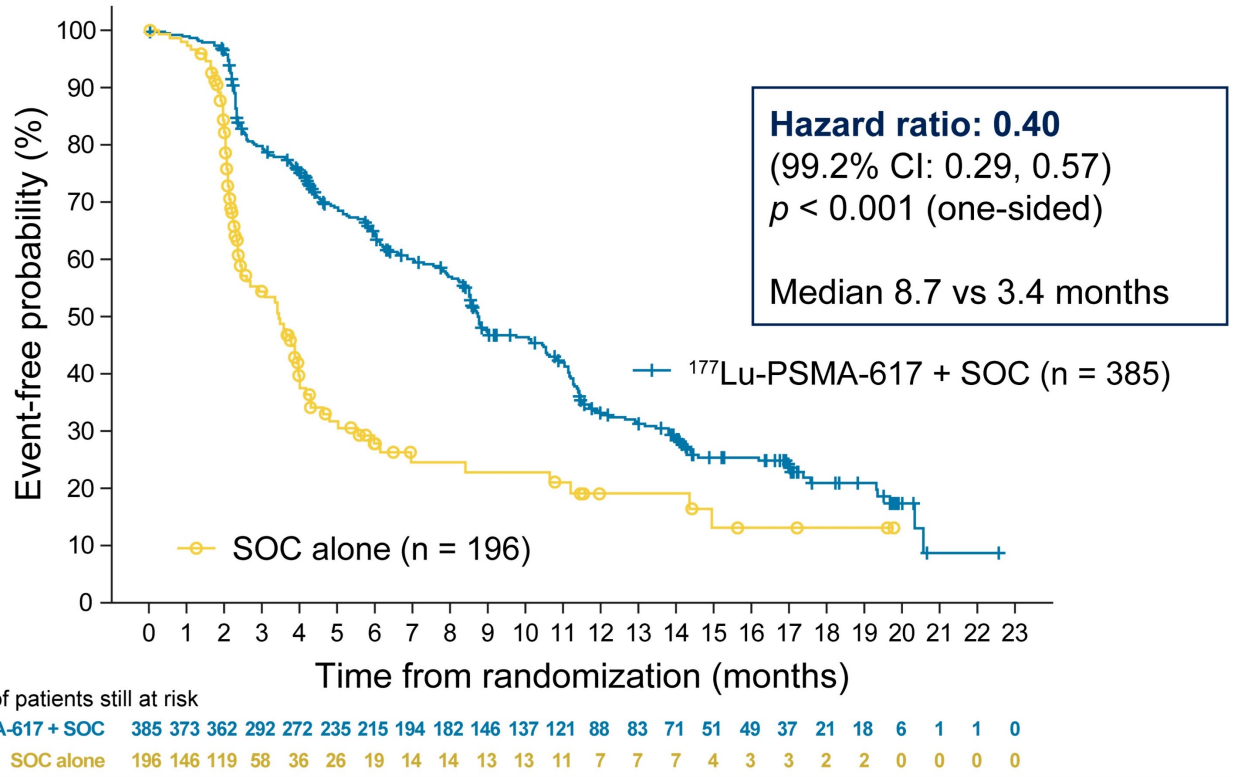
Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

Primary analysis

rPFS analysis set (n = 581)



Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SOC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

DNA Damage Response (DDR) Pathways

- **Normal cells repair SSB in DNA via BER (utilize PARP)**

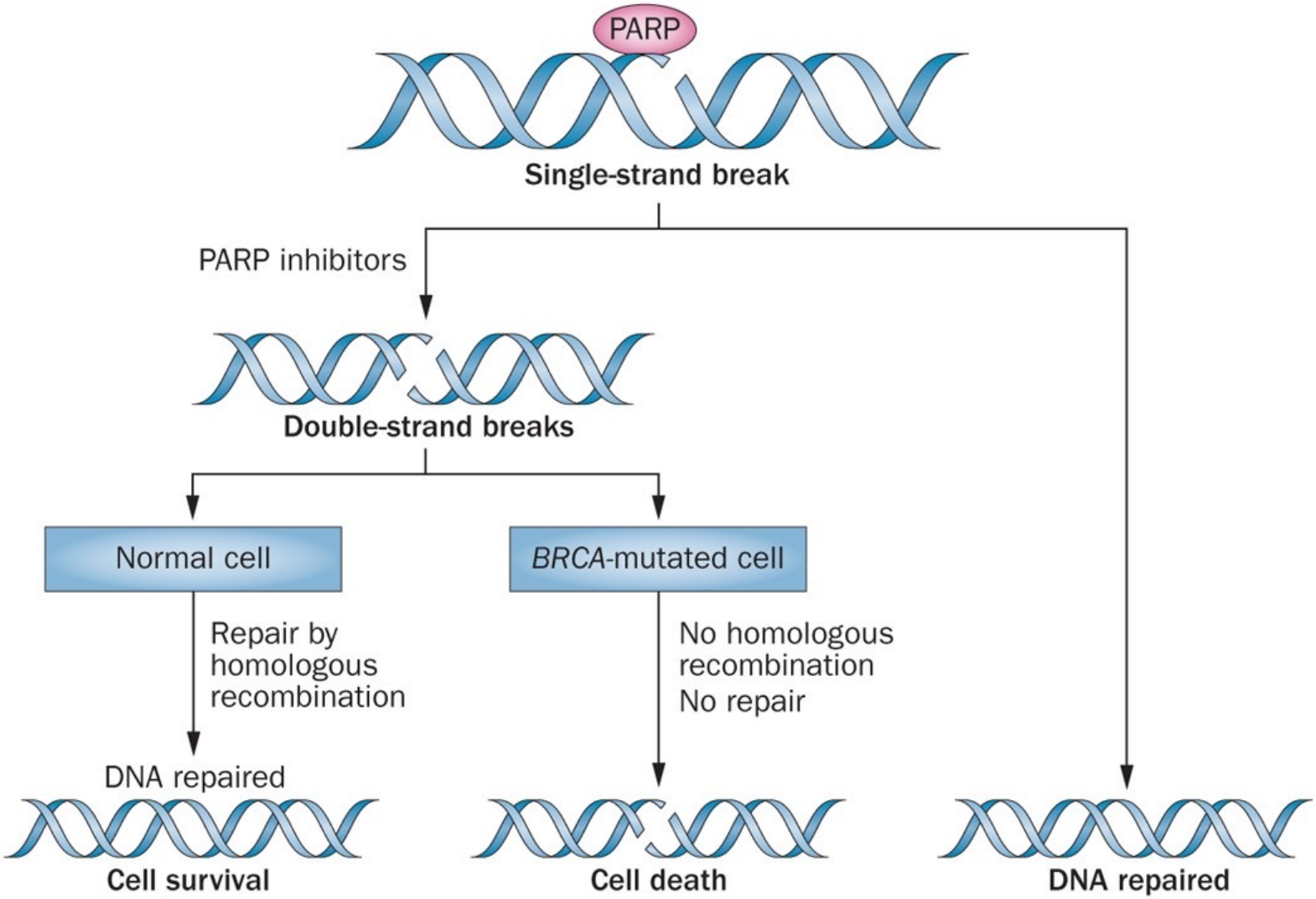
- **Normal cells repair DSB in DNA via Homologous Recombination (HR)**
  - BRCA1, BRCA2, ATM, others

- **SSB repair pathways can compensate for DSB pathways (and vice versa)**
  - If have *HR defects* (eg: BRCA1/2, ATM mutations) then cells up to 1000 x more sensitive to PARP inhibitors (bi-allelic loss)

- **DDR defects in prostate cancer – can treat with PARP inhibitors**
  - up to 20% advanced CRPC
  - up to 5% germline mutations in BRCA

- **There is cross-talk between AR signaling and DDR pathways, which could be exploited**

- **Cross-talk between PARP and cell cycle (eg: RB/E2F1)**


PARP
Single-strand break
PARP inhibitors
Double-strand breaks
Normal cell
BRCA-mutated cell
Repair by homologous recombination
No homologous recombination
No repair
DNA repaired
Cell survival
Cell death
DNA repaired

PARP Inhibitors in Metastatic CRPC

- PROfound Trial: Olaparib
  - Olaparib vs enzalutamide or abiraterone, 2:1 randomization
  - BRCA1/2, ATM mutations
  - Primary endpoint: rPFS
    - 7.4 months vs 3.6 months, HR 0.34 (0.25-0.47)
  - Secondary endpoint: OS
    - 18.5 months vs 15.1 months

- Triton 2 Trial: Rucaparib
  - Phase 2 trial in mCRPC post next gen hormonal agent and one prior chemotherapy regimen
  - BRCA1/2 mutated
  - Primary endpoints: OFF, PSA response rates

Presentation number 5004

2023 ASCO ANNUAL MEETING

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer harboring homologous recombination repair gene alterations (HRR-deficient population)

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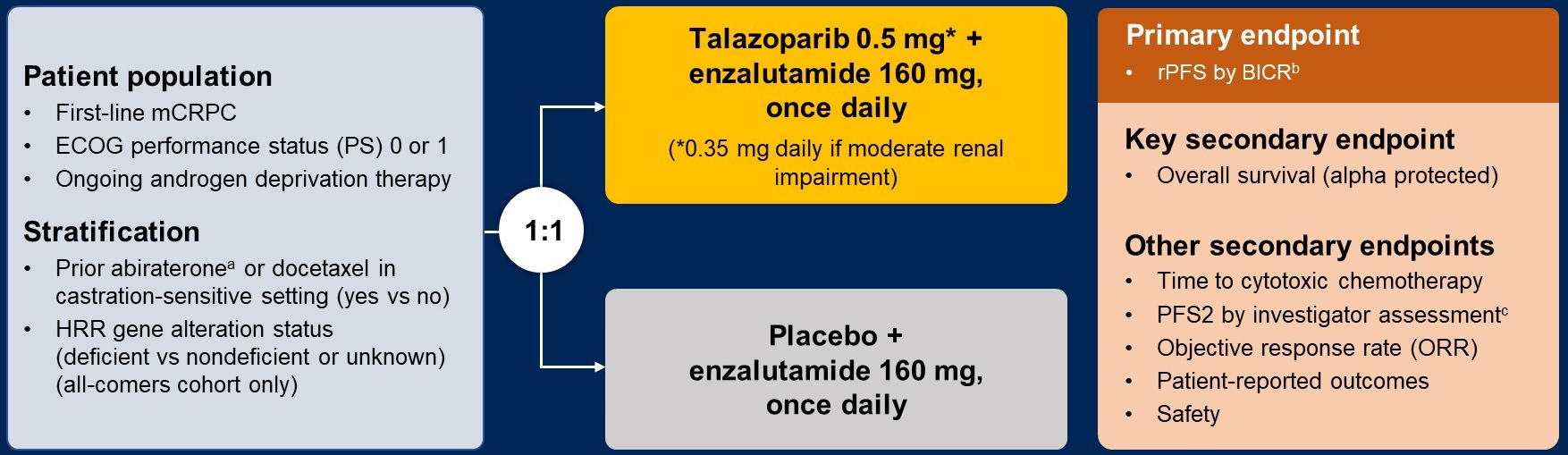
ClinicalTrials.gov identifier: NCT03395197.
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study

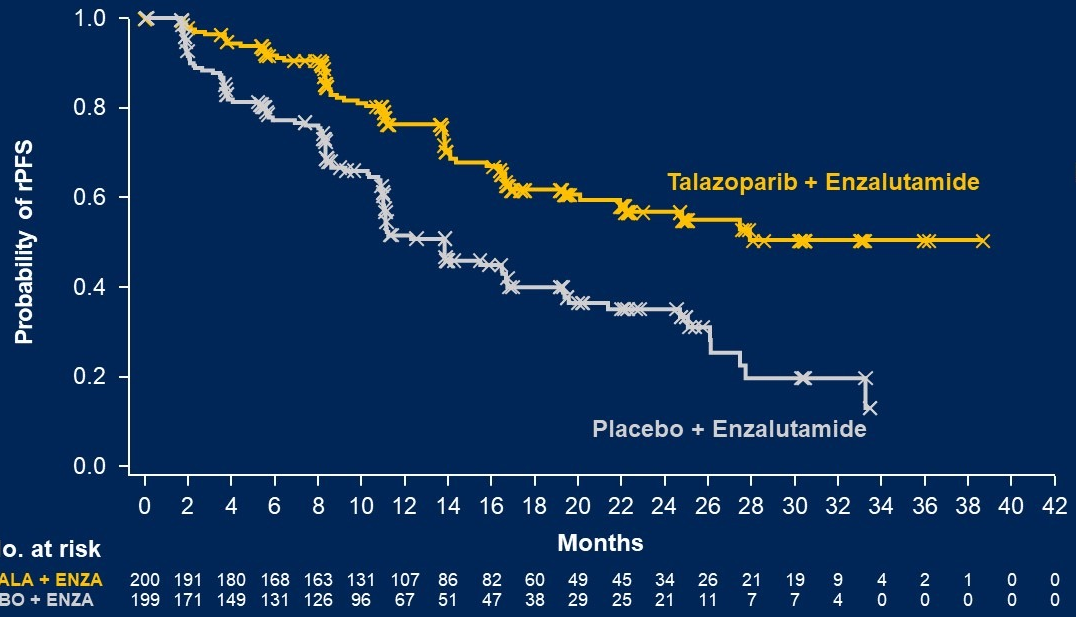


Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx

BICR=blinded independent central review; rPFS=radiographic progression-free survival.
[a]One patient in each treatment arm received prior orteronel. [b]Per RECIST version 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). [c]Time from randomization to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurred first.

TALAPRO-2 HRR-Deficient Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 55% reduced risk of progression or death



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	66	104
Median (95% CI), months	Not reached (NR) (21.9–NR)	13.8 (11.0–16.7)
HR (95% CI)	0.45 (0.33–0.61); *P* < 0.0001	

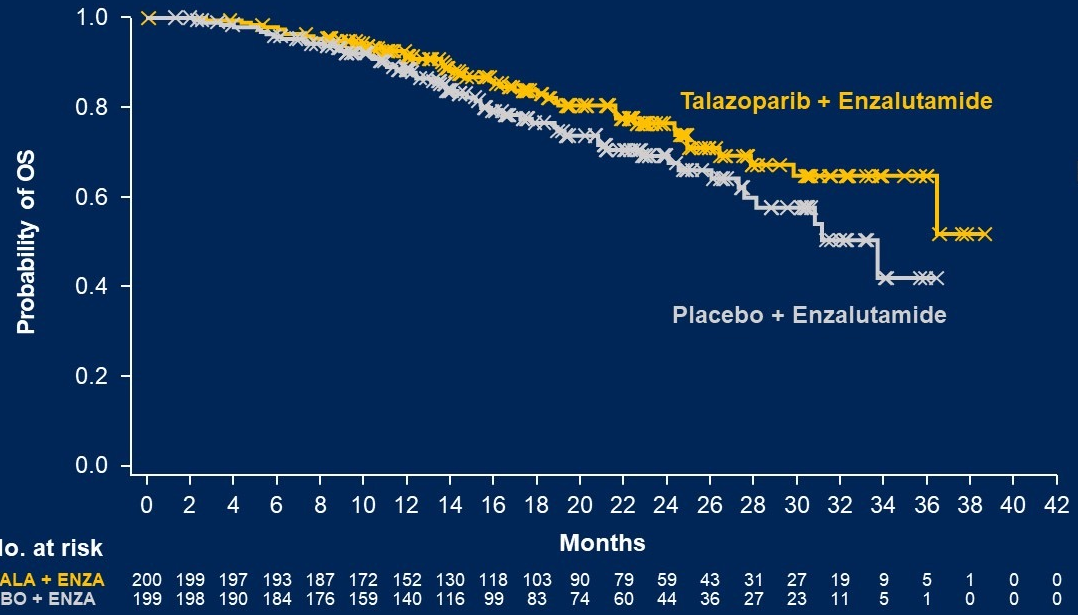
Median follow-up for rPFS was 17.5 and 16.8 months, respectively

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.48 (95% CI, 0.33–0.67); *P* < 0.0001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

TALAPRO-2 HRR-Deficient: Overall Survival (Interim Analysis)

Overall survival data are immature (24% maturity overall)



	TALA + ENZA (N=200)	PBO + ENZA (N=199)
Events, n	43	53
Median (95% CI), months	NR (36.4–NR)	33.7 (27.6–NR)
HR (95% CI)	HR 0.69 (95% CI, 0.46–1.03) *P* = 0.068	

***BRCA*m HR 0.61 (95% CI, 0.31–1.23; *P* = 0.16)**
non-*BRCA*m HR 0.71 (95% CI, 0.43–1.18; *P* = 0.18)

18 patients in the control arm and 3 patients in the talazoparib arm subsequently received olaparib

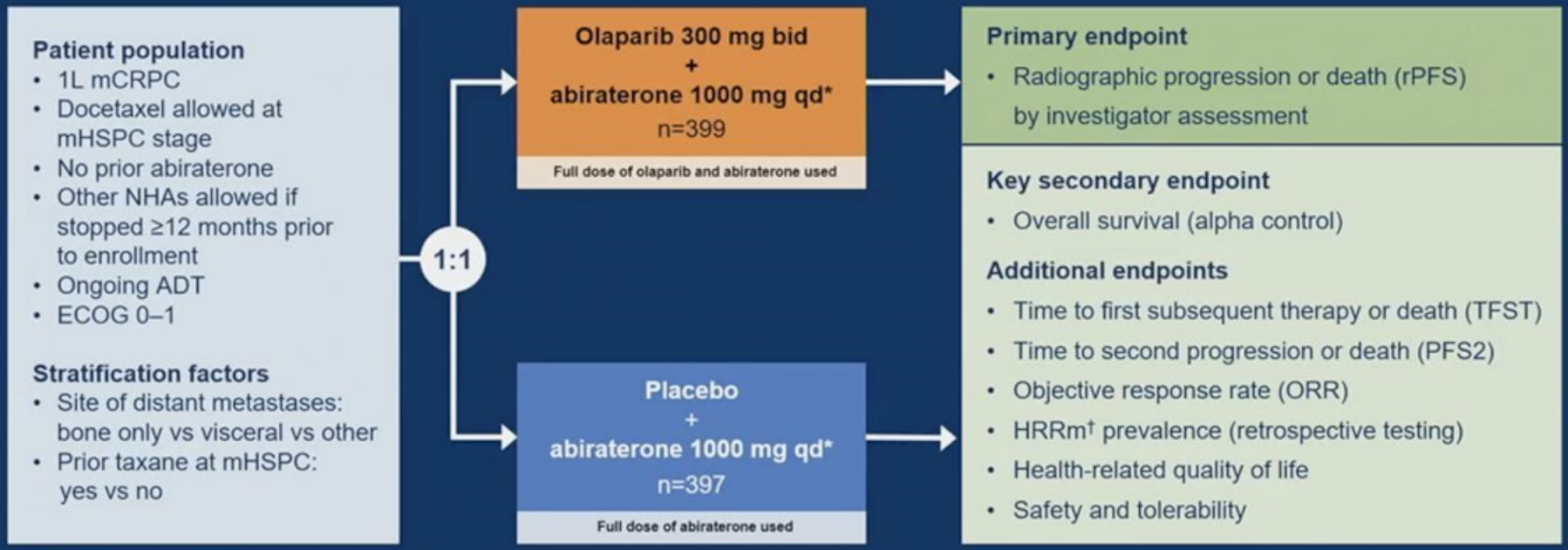
Randomized Trials with PARP Inhibitors in mCRPC

- TALAPRO-2: Talazoparib + Enzalutamide - 1st line mCRPC (HRRm, non-HRRm)

- PROpel: Olaparib + Abiraterone - 1st line mCRPC (HRRm, non-HRRm)

- TRITON-3: Rucaparib vs Investigators Choice (Docetaxel or NHA) in HRRm after failure of one NHA

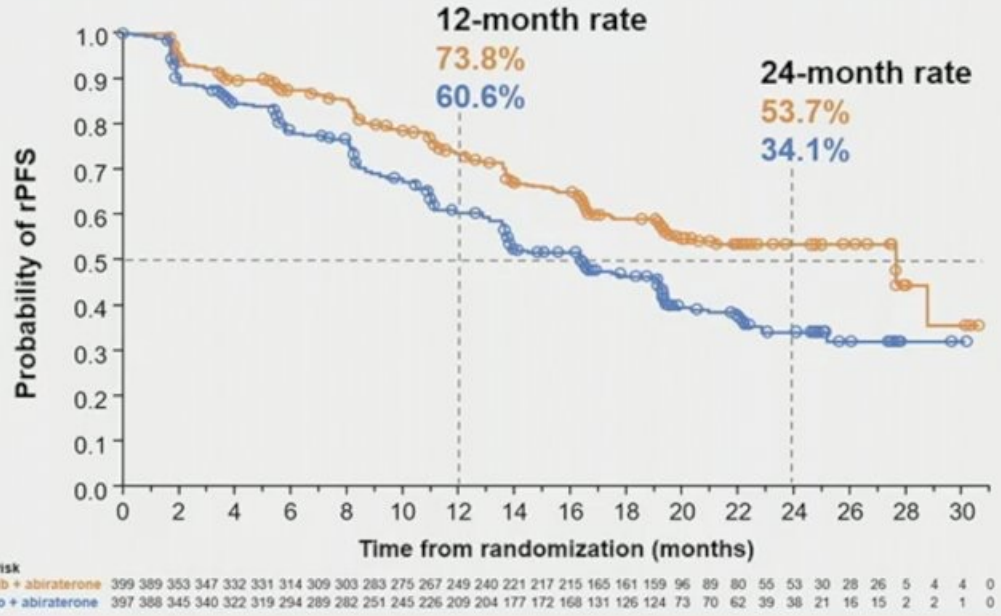
PROpel: a global randomized double-blind phase III trial



First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
Please access the ***Supplement*** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

PROpel: rPFS by blinded independent central review*

39% risk reduction of progression or death with olaparib + abiraterone
Highly consistent with the primary analysis



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

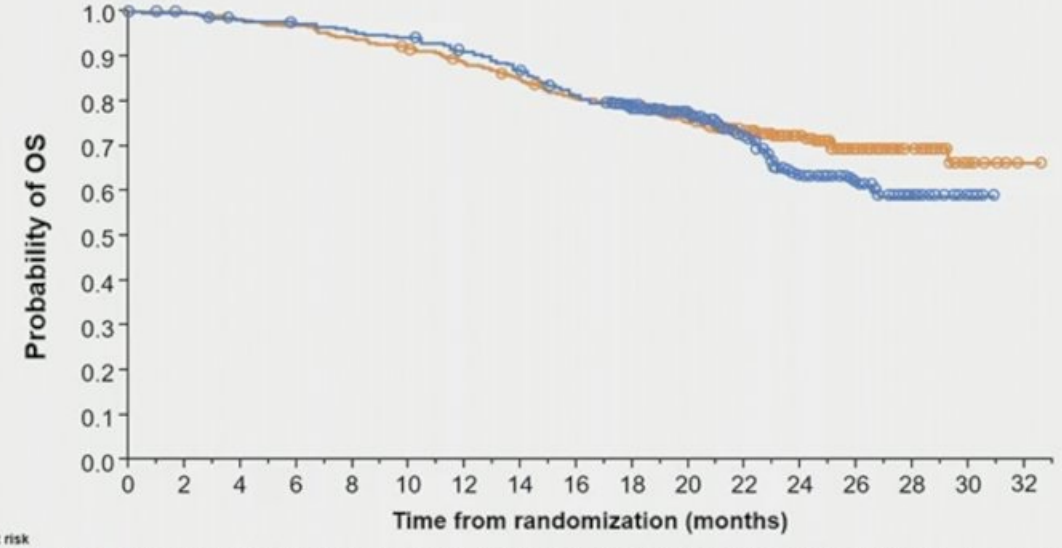
Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

*Predefined sensitivity analysis. †Nominal. ‡In combination with prednisone or prednisolone

PRESENTED BY: Professor Fred Saad

PROpel: overall survival

28.6% maturity; trend towards improved OS with olaparib + abiraterone



No. at risk

Olaparib + abiraterone	399	398	398	394	391	387	385	379	374	369	364	359	349	343	333	322	316	313	290	263	231	193	159	135	116	92	73	51	37	24	11	4	1	0
Placebo + abiraterone	397	394	392	386	385	383	381	377	374	371	368	363	353	345	335	322	314	308	286	258	223	186	151	121	104	88	63	44	22	13	6	0	0	0

	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	107 (26.8)	121 (30.5)
Median OS (months)	NR	NR
HR (95% CI)	0.86 (0.66–1.12) *P*=0.29	

Pre-specified 2-sided alpha: 0.001

Events: 228
NR, not reached.

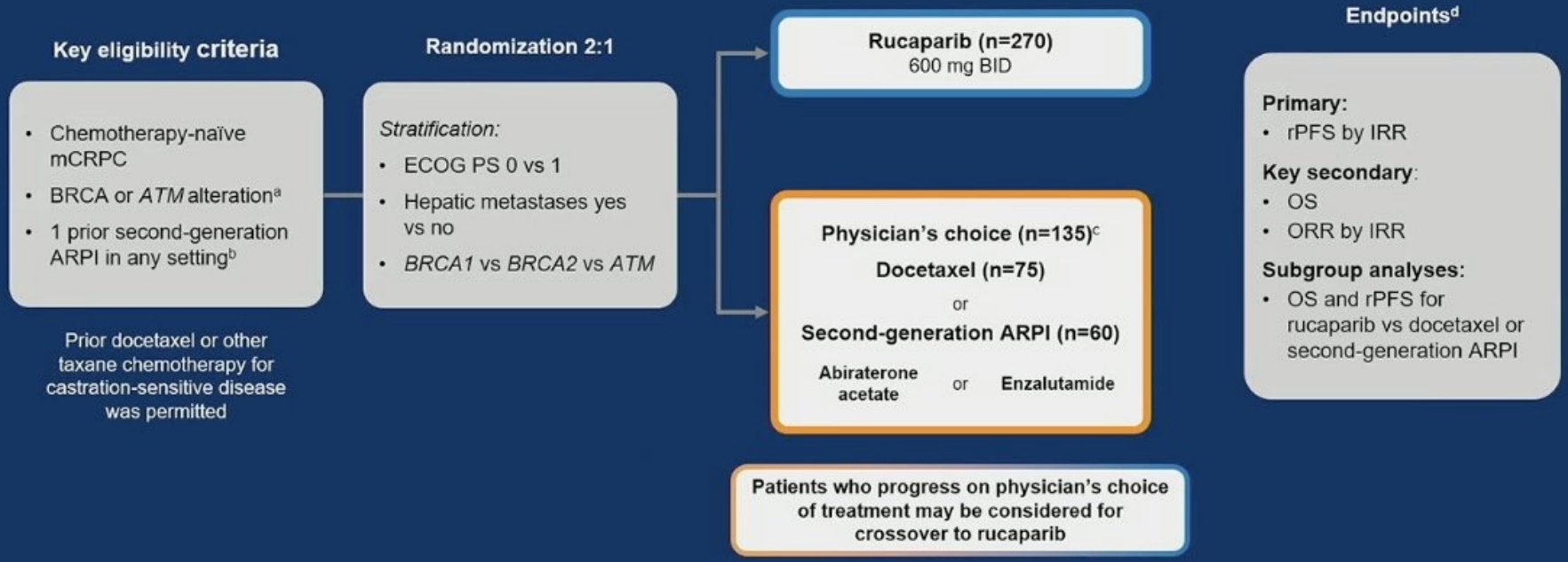
Randomized Trials with PARP Inhibitors in mCRPC

- TALAPRO-2: Talazoparib + Enzalutamide - 1st line mCRPC (HRRm, non-HRRm)

- PROpel: Olaparib + Abiraterone - 1st line mCRPC (HRRm, non-HRRm)

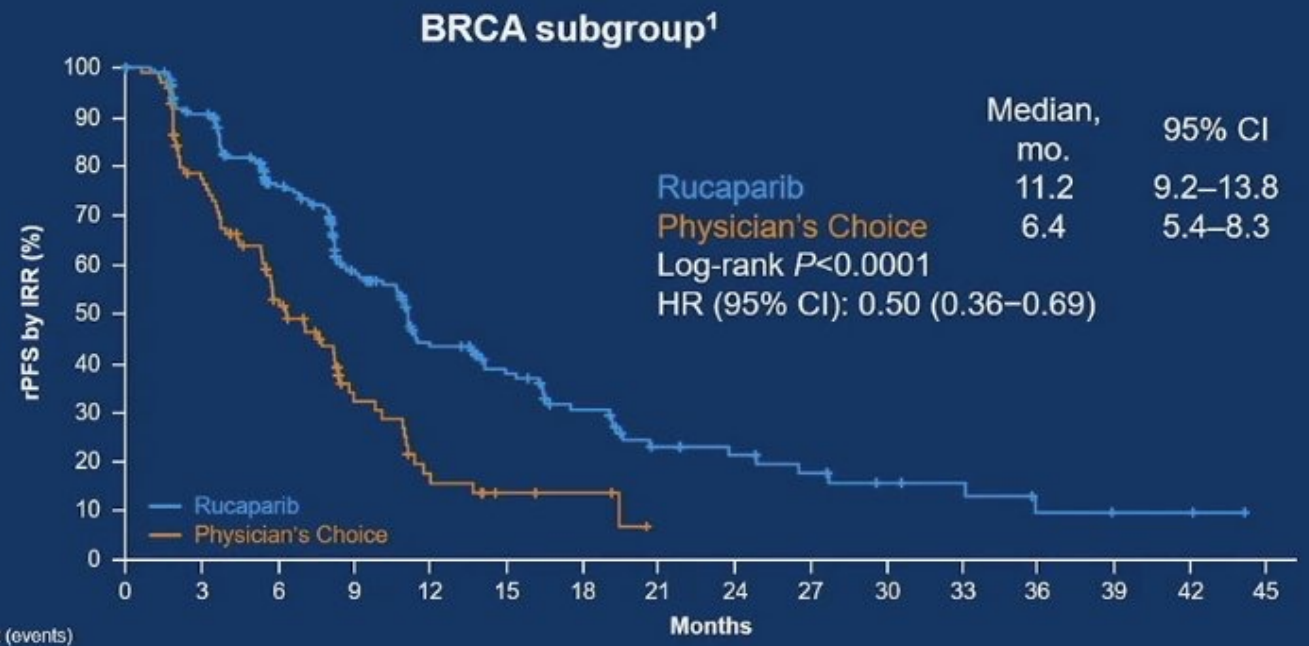
- TRITON-3: Rucaparib vs Investigators Choice (Docetaxel or NHA) in HRRm after failure of one NHA

TRITON3 Study Design



Visit cutoff date: 25 August 2022. [a]Determined by Foundation Medicine testing of tissue or plasma. [b]Protocol amendment 19 June 2018; patients' qualifying second-generation ARPI could be in any setting. [c]If chosen, patients received whichever second-generation ARPI had not yet been received. Docetaxel: 75 mg/m^2 Q21D, 10 cycles max; Abiraterone acetate: 1000 mg QD; Enzalutamide: 160 mg QD; [d]Tumor assessments were conducted at baseline and every 8 weeks for 24 weeks, then every 12 weeks, via CT/MRI and technetium-bone scans. [e]84 patients had IRR-confirmed progression, including 3 who were later re-evaluated as having non-progressive disease by IRR. ARPI, androgen receptor pathway inhibitor; BID, twice daily; BRCA, *BRCA1* and *BRCA2*; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostrate cancer; OS, overall survival; Q21D, every 21 days; QD, daily; rPFS, radiographic progression-free survival.

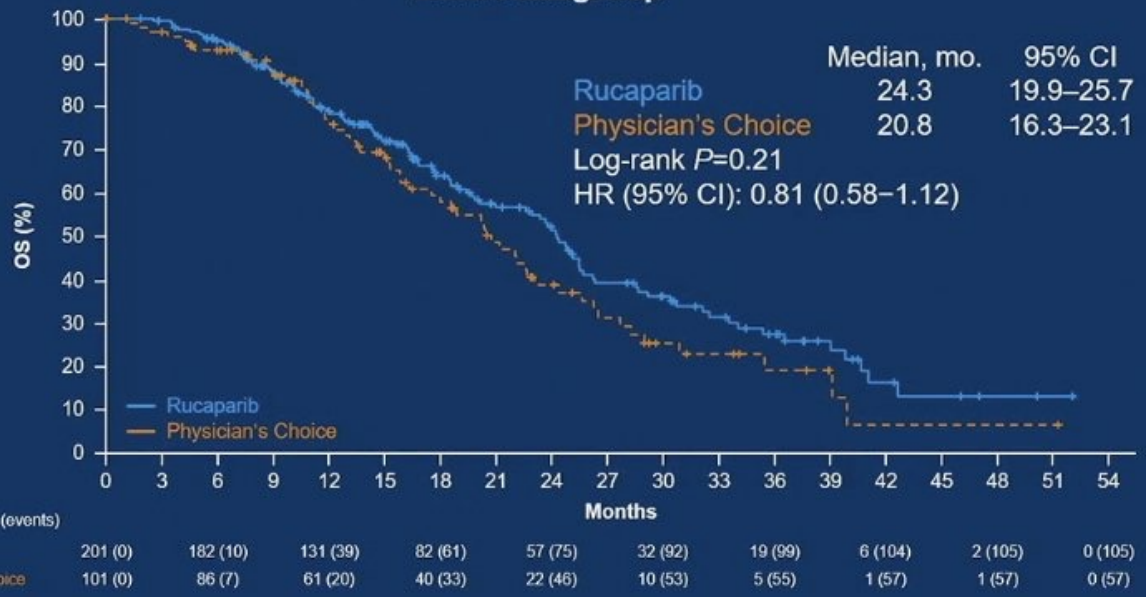
Radiographic PFS



Visit cutoff date: 25 August 2022. BRCA subgroup data maturity (rucaparib vs physician's choice): 182/302 (60.3%). 1. Bryce et al. Presented at the 2022 PCF Annual Retreat.
BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival; rPFS, radiographic progression-free survival.

Interim OS

BRCA subgroup



Patients at risk (events)

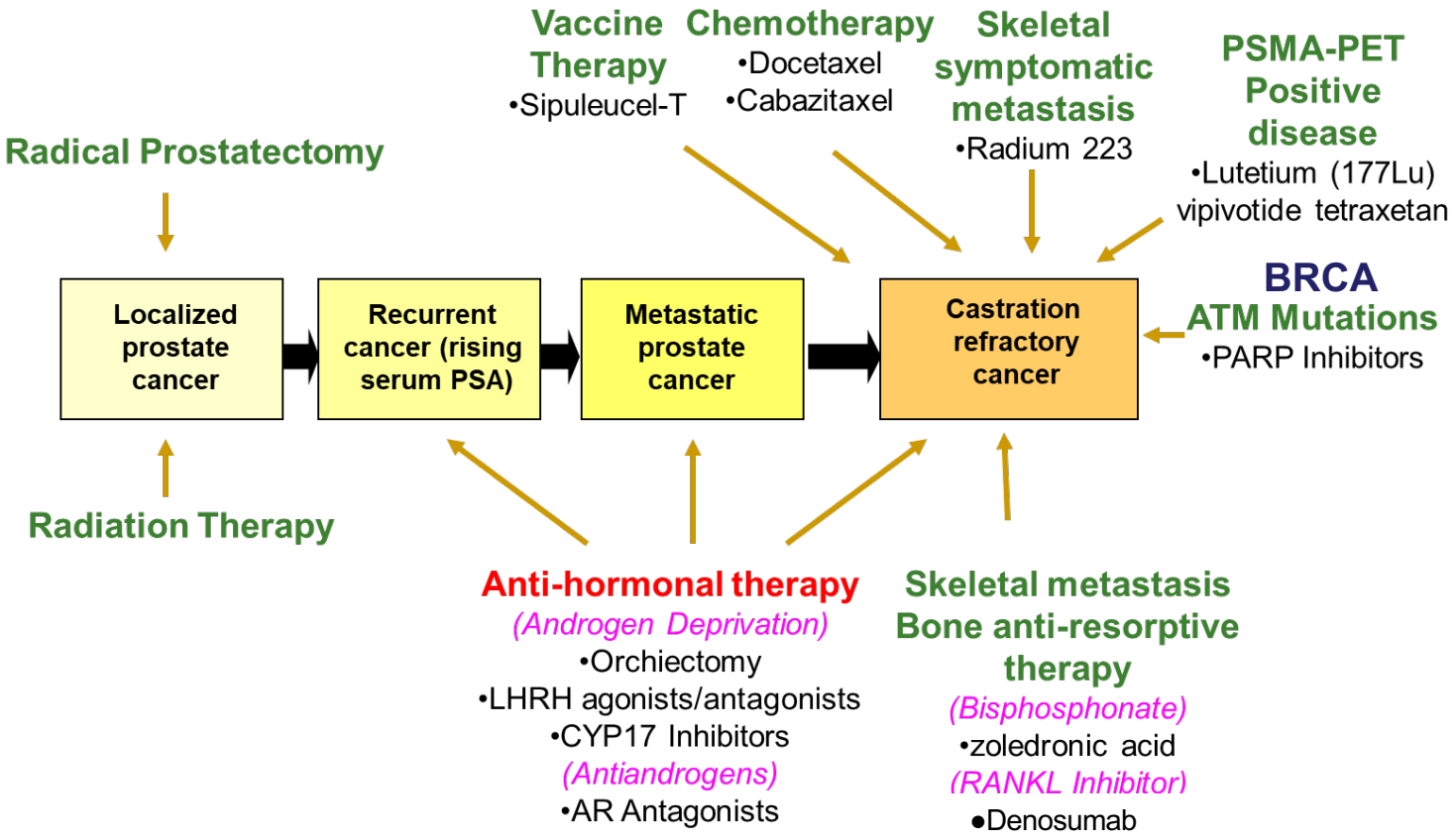
Rucaparib	201 (0)	182 (10)	131 (39)	82 (61)	57 (75)	32 (92)	19 (99)	6 (104)	2 (105)	0 (105)
Physician's Choice	101 (0)	86 (7)	61 (20)	40 (33)	22 (46)	10 (53)	5 (55)	1 (57)	1 (57)	0 (57)

ITT population

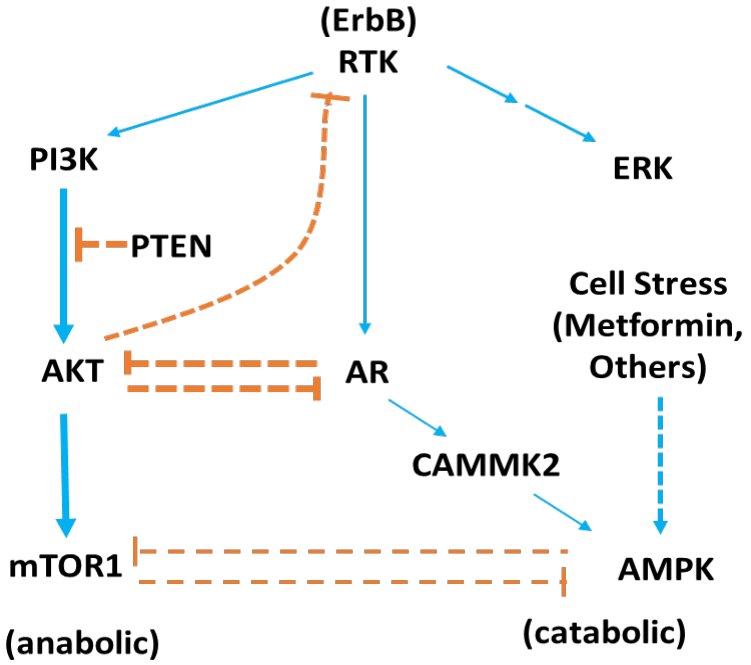
	Rucaparib (n=270)	Physician's Choice (n=135)
Median OS, mos (95% CI)	23.6 (19.7–25.0)	20.9 (17.5–24.4)
Log-rank *P*	0.67[a]	
HR (95% CI)	0.94 (0.72–1.23)	

- BRCA subgroup data maturity (rucaparib vs physician's choice): 162/302 (53.6%)
- Target maturity for final analysis: 70%

[a]Nominal. Visit cutoff date: 25 August 2022. BRCA, *BRCA1* and *BRCA2*; HR, hazard ratio; ITT, intent to treat; OS, overall survival.



Prostate cancer progression and treatment



ErbB, AKT, AR cross-signaling in AR-expressing prostate cancer cells.

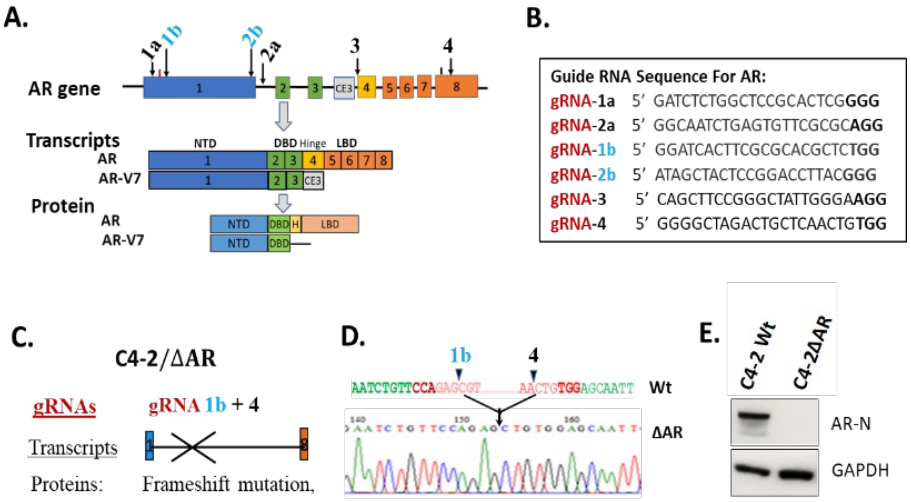
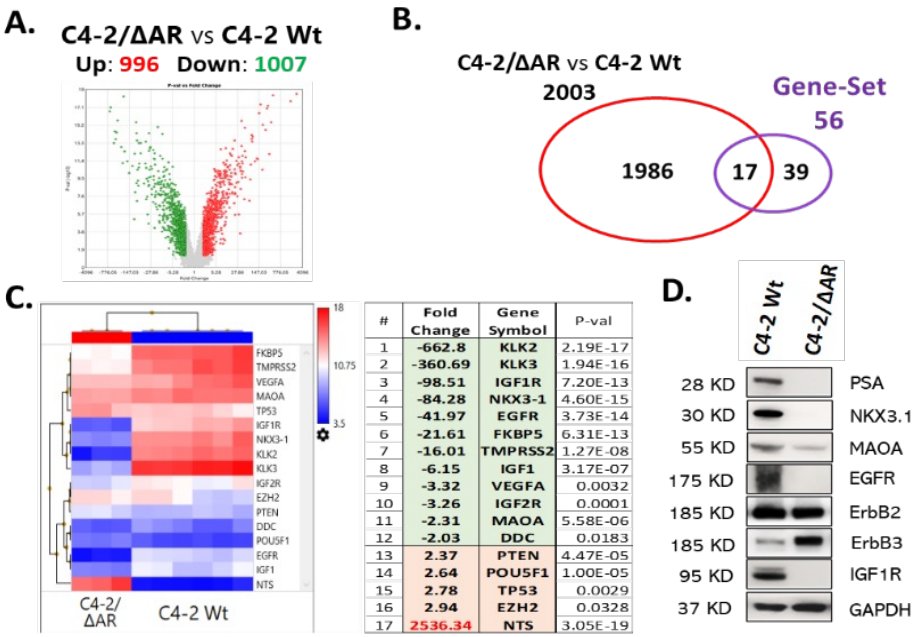
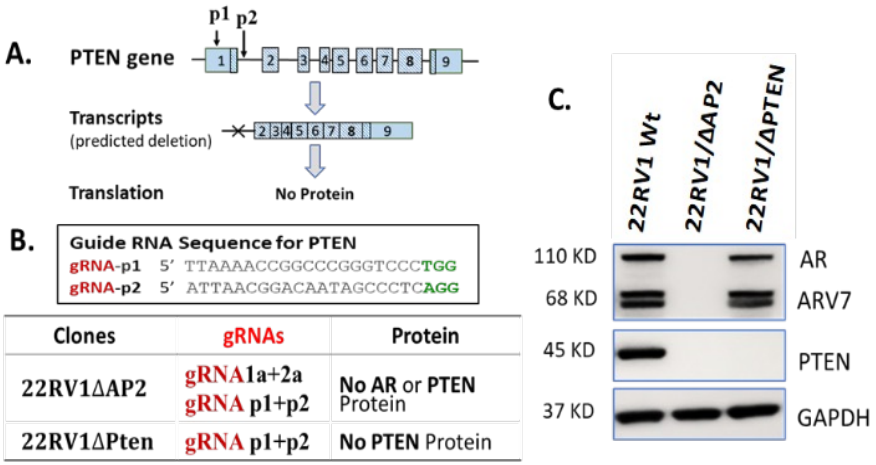


Fig 10. C4-2/ΔAR cells, generated by AR gene knock out in C4-2 cells. A) Schematic representation of AR gene, canonical exons and cryptic exon3 (CE3); arrows show gRNA target sites. B) gRNA sequences. C) gRNAs used to knock out AR in C4-2 cells. D, E) AR knock out in C4-2/ΔAR clone confirmed by DNA sequencing and western blot, respectively.



#	Fold Change	Gene Symbol	P-val
1	-662.8	KLK2	2.19E-17
2	-360.69	KLK3	1.94E-16
3	-98.51	IGF1R	7.20E-13
4	-84.28	NKX3-1	4.60E-15
5	-41.97	EGFR	3.73E-14
6	-21.61	FKBP5	6.31E-13
7	-16.01	TMPRSS2	1.27E-08
8	-6.15	IGF1	3.17E-07
9	-3.32	VEGFA	0.0032
10	-3.26	IGF2R	0.0001
11	-2.31	MAOA	5.58E-06
12	-2.03	DDC	0.0183
13	2.37	PTEN	4.47E-05
14	2.64	POU5F1	1.00E-05
15	2.78	TP53	0.0029
16	2.94	EZH2	0.0328
17	2536.34	NTS	3.05E-19

Fig 11. Analysis of C4-2/ΔAR clone. RNA expression data analyzed using TAC software. A) Volcano plot; 2003 genes differentially expressed between Wt and AR knock out clone. B) Venn diagram. 17 genes (passed Gene-Set filter) in common with the pre-defined 56 gene panel. C) Heat map of the 17 genes in B. D) Western blot, protein expression of selected genes.



Clones	gRNAs	Protein
22RV1ΔAP2	gRNA1a+2a gRNA p1+p2	No AR or PTEN Protein
22RV1ΔPten	gRNA p1+p2	No PTEN Protein

Fig 17. PTEN knock out and PTEN + AR^{FL}/ARV7 knockouts in 22RV1 cells. A) Schematic representation of PTEN gene. B) gRNAs p1, p2 used to knock out PTEN to generate clone 22RV1/ΔPTEN; gRNAs 1a, 2a (Fig 10B), and gRNAs p1, p2 used to knock out both AR^{FL}/ARV7 and PTEN to generate clone 22RV1/ΔAP2. C) Western blot confirmation of the respective knockouts.