

The New and the Old in Advanced Prostate Cancer



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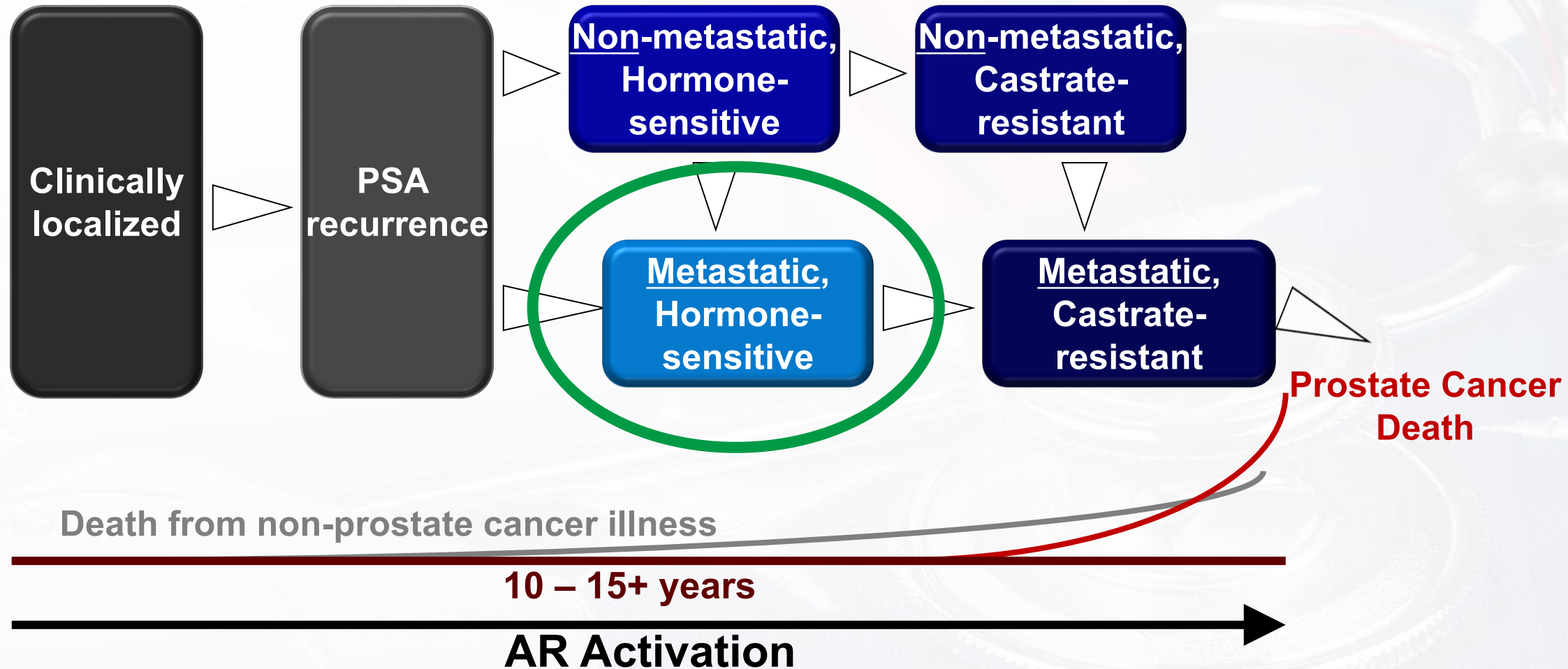
Three Main Objectives

Management of Castrate Sensitive Prostate Cancer

Advances in Castrate Resistant Prostate Cancer

Novel Therapies and Advances

Clinical States of Prostate Cancer

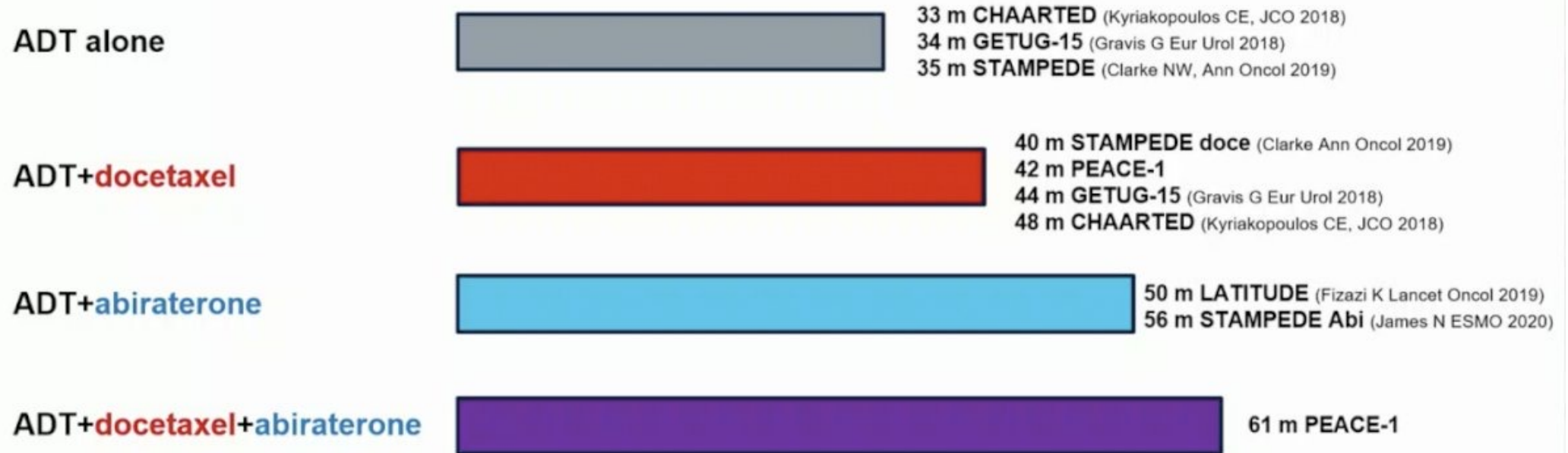


Metastatic Hormone Sensitive Prostate Cancer

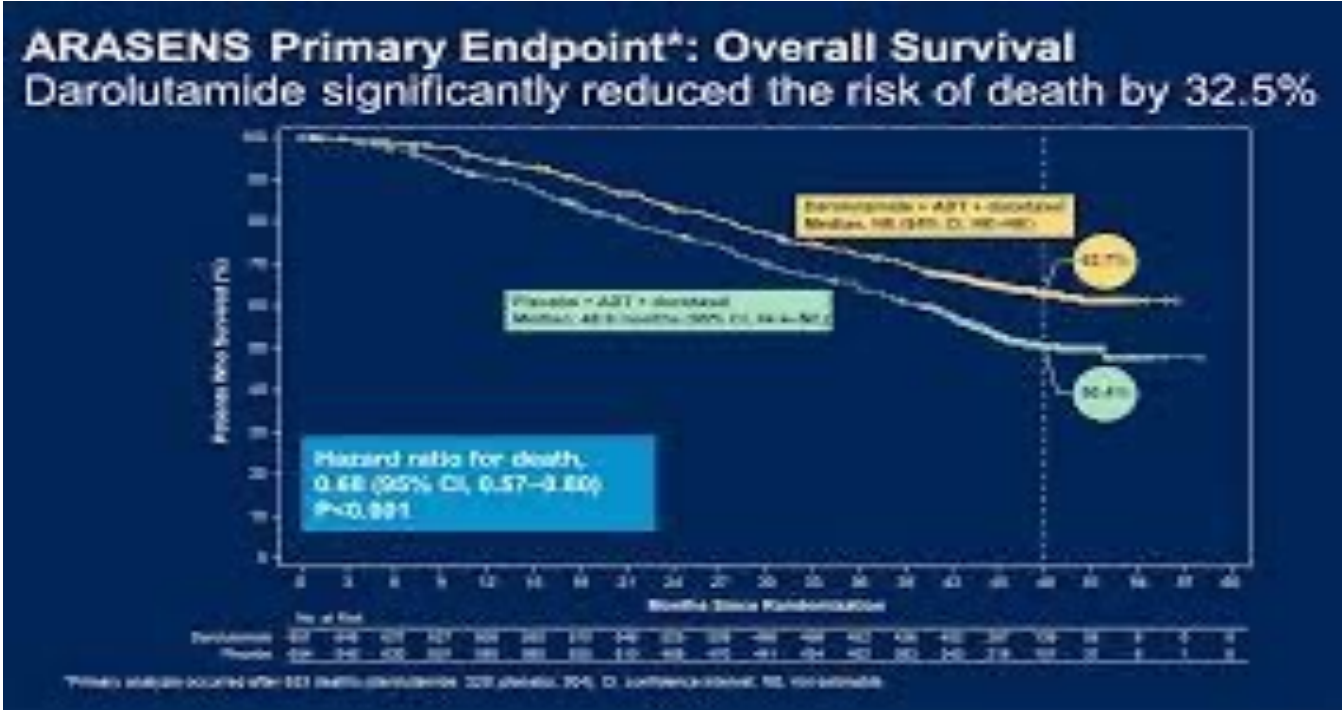
Study	Agent/s	PFS/OS	P value	Key adverse Events
TITAN	Apalutamide Vs Placebo	NR 22.1 mo	<0.0001 HR=0.48	Rash, mental changes, fractures
Enzamet	Enzalutamide Vs Placebo	NR 19 mo	<0.001 HR=0.39	Seizures Fatigue falls
Latitude	Abiraterone Vs Placebo	53.3 mo 36.5 mo	<0.001 HR=0.47	Hypertension Hypokalemia Edema
CHAARTED	ADT + Docetaxel Vs ADT	57.6 mo 44 mo	<0.001 HR=0.61	Febrile neutropenia Neuropathy Alopecia

PEACE-1 OS results in the context of recent data

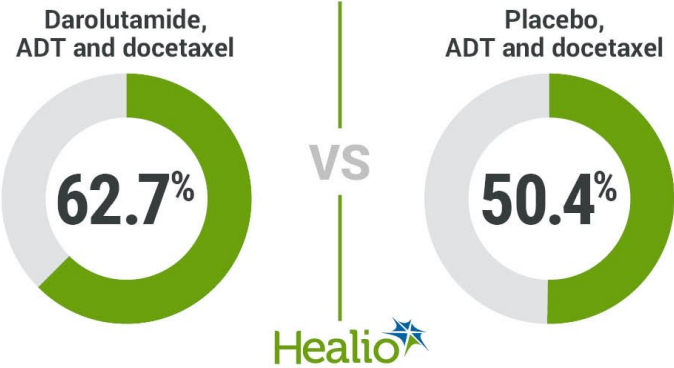
Median Overall Survival (*de novo* High-Volume mCSPC)



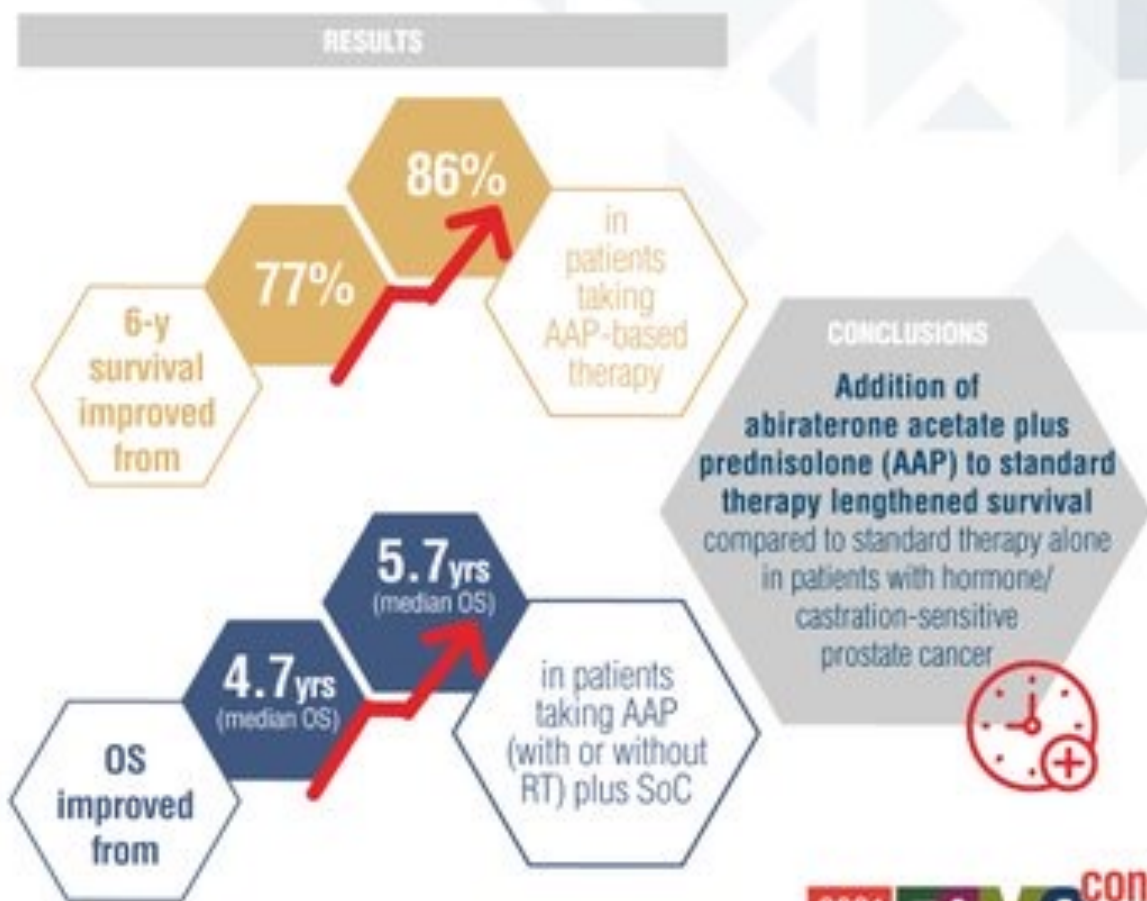
Triplet Therapy in mHSCPC: ARASENS: ADT + darolutamide + chemo



4-year OS in the ARASENS trial

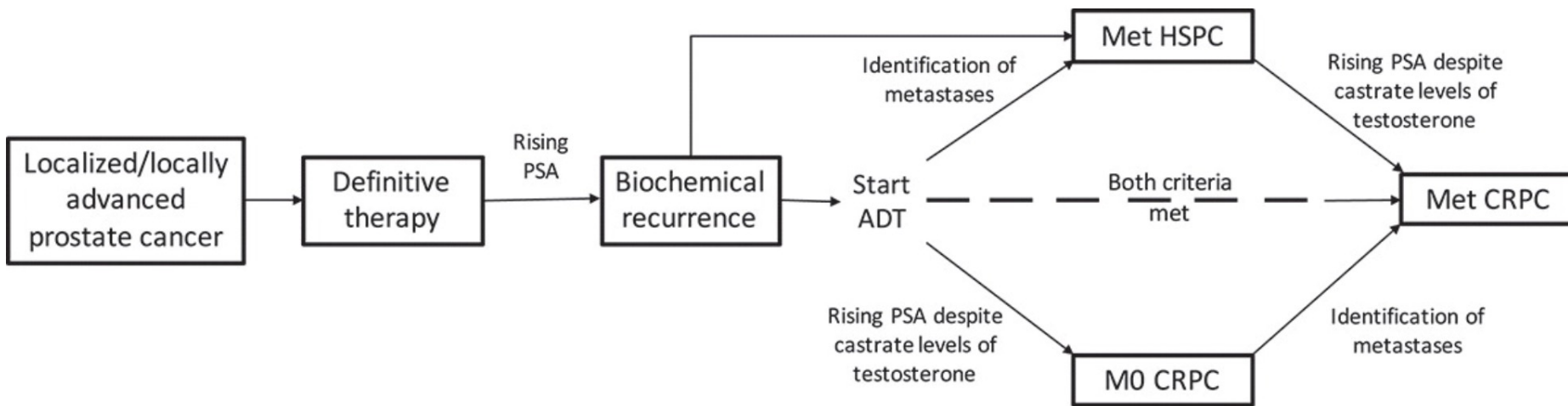


New combination of old drugs improves survival in patients with prostate cancer



Notes:
G. Attard, et al. LBA 4 presented at ESMO Congress 2021. K. Fizazi, et al. LBA 5 presented at ESMO Congress 2021

Non-Metastatic Castrate-Resistant Prostate Cancer (M0 nmCRPC)



- Predictor of outcomes in nmCRPC^[1,2]
 - Longitudinal study population: 13,552 Veterans with nmCRPC
 - Increased risk of death in men with nmCRPC was associated with:
 - Higher log PSA at baseline
 - Shorter PSADT
 - Development of metastases

Non Metastatic Castrate Resistant Prostate Cancer

Study	Agent	MFS	P value	Key adverse Events
SPARTAN	Apalutamide Vs Placebo	40.5 mo 16.2 mo	<0.001 HR=0.28	Rash, seizures Mental changes Cardiac events
PROSPER	Enzalutamide Vs Placebo	36.6 mo 14.7 mo	<0.001 HR=0.29	Seizures Hypertension Cardiac events
ARAMIS	Darolutamide Vs Placebo	40.4 mo 18.4 mo	<0.001 HR=0.41	No seizure activity Fatigue noted

Addressing unmet medical needs for men with nmCRPC...

Men diagnosed with nmCRPC are typically active and often have no symptoms. Therefore, the goals of treatment are to:



Extend survival

Improving overall survival

is as vital for men with nmCRPC as at all stages of the prostate cancer continuum^{3,6}



Delay disease progression

nmCRPC is a critical point in the disease progression. About **one-third of men with nmCRPC go on to develop metastases, within two years,**^{3,7} associated with reduced quality of life and increased morbidity and healthcare costs



Preserve quality of life

Negative treatment side effects can compromise quality of life, overall well-being, and compliance with the prostate cancer treatment, as well as with other medications that are typical for men with nmCRPC^{4,5,8}

Therapy Options for CRPC: agents with level I evidence

nmCRPC

- Apalutamide
- Enzalutamide
- Darolutamide

**Metastasis Free
Survival and Overall
Survival**

mCRPC
Therapy
selection
depends on
prior therapy

- Sipuleucel T
- Abiraterone
- Enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223

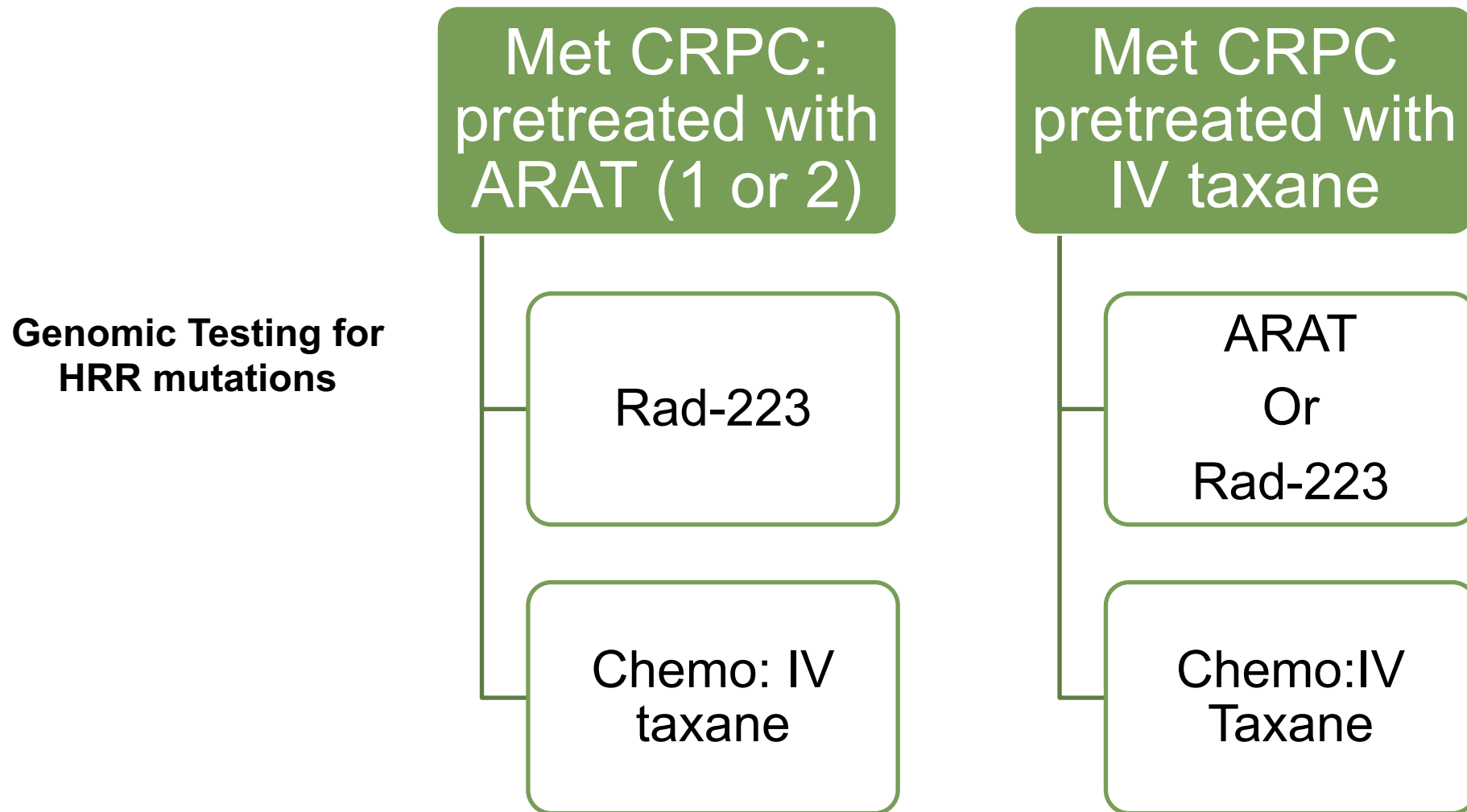
Overall Survival

Summary of Approved Therapies with Survival Benefit in mCRPC

Agent	Indication	Route Schedule	Cortico-steroids	Symptoms	Contra-indications	PSA Response	Median OS Benefit, Mos
Sipuleucel-T	Pre/post docetaxel	IV every 2 wk x 3	no	asymptomatic, minimally sx	narcotics for pain, liver mets	No	4.1
Abiraterone	Pre/post docetaxel	oral, empty stomach	yes*	not specified	severe liver dysfx, low K, heart failure	Yes	Post-doc: 4.6 Pre-doc: 4.4
Enzalutamide	Pre/post docetaxel	oral	no	not specified	seizures	Yes	Post-doc: 4.8 Pre-doc: 4.0
Docetaxel	mCRPC	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Cabazitaxel	Post docetaxel	IV every 3 wk	yes*	not specified	moderate liver dysfx, cytopenias	Yes	2.4
Radium-223	Post docetaxel or not fit for docetaxel	IV, every 4 wks for 6 doses	not required	symptomatic bone metastases	visceral mets	NR	3.6

* In clinical trials and on FDA label.

Sequencing Decisions in mCRPC: Pretreated population



Genomic Testing in mCRPC: Actionable mutations

→ DNA repair mutations such as BRCA1, BRCA2, ATM, PALB2, CHK

Use PARP inhibitors

→ MSI high- use pembrolizumab

→ Tumor mutation burden >10- Pembrolizumab

→ ARV7 mutation: Unlikely to respond to abiraterone or enzalutamide

→ PTEN loss: Ipatasertib is being evaluated

→ Other PI3 kinase inhibitors are being evaluated

DNA Damage Repair as a Therapeutic Target

- BRCA1/2 and others are proteins that repair double-strand DNA breaks
- When the gene for these proteins are mutated, the change can lead to errors in DNA repair that cause neoplastic growth
- However, when subjected to enough damage at one time, the altered gene can cause death of cells
- PARP1 is a protein that is important for repairing single-strand breaks
- Drugs that inhibit PARP1 cause multiple double-strand breaks, and because these double-strand breaks cannot be efficiently repaired, cell death results:

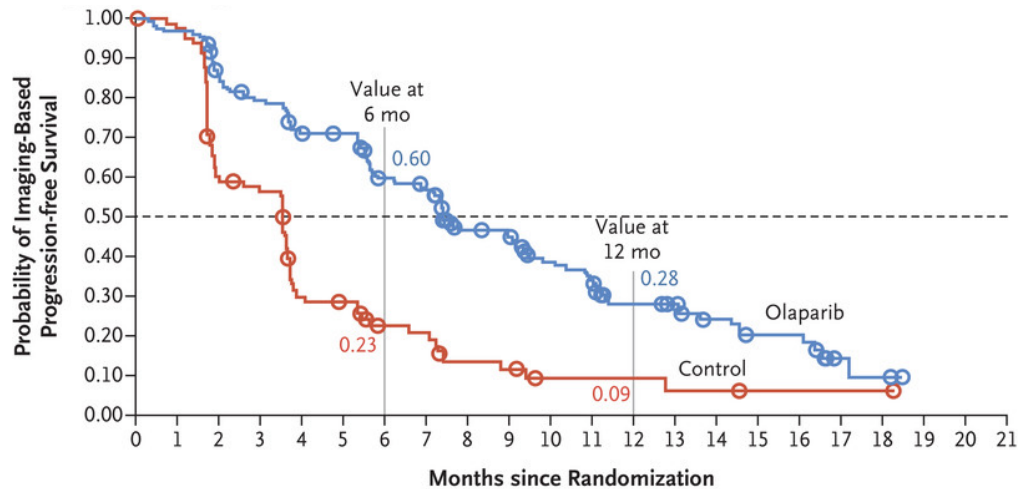
“SYNTHETIC LETHALITY”

Phase III PROfound: Olaparib vs Physician's Choice in mCRPC

Imaging-Based PFS in Cohort A

Median rPFS, months

Olaparib 7.4
 Control 3.6
 HR, 0.34 (95%CI, 0.25-0.47); $P < 0.0001$



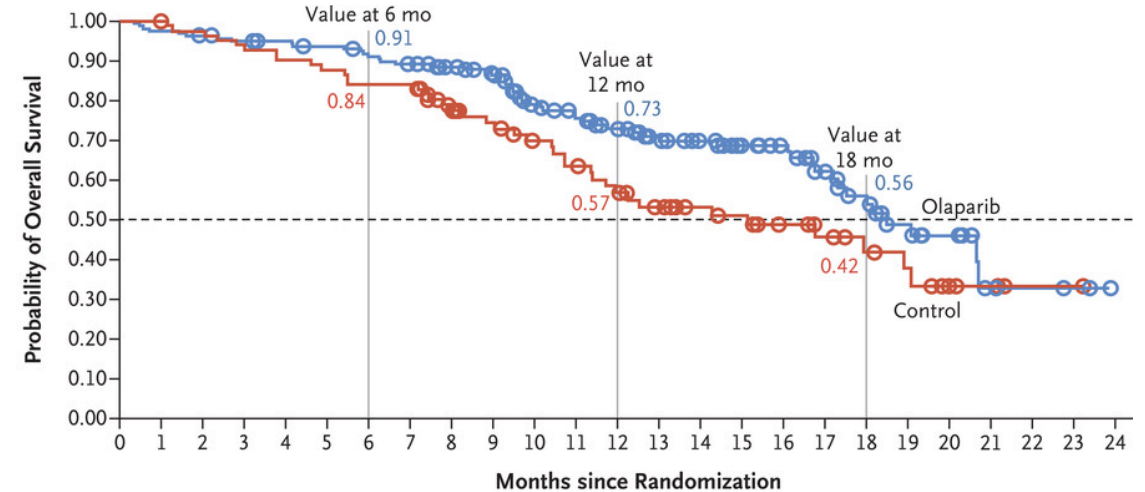
No. at Risk

Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Control	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

Interim OS in Cohort A

Median Interim OS, months

Olaparib 18.5
 Control 15.1
 HR, 0.64 (95%CI, 0.43-0.97); $P=0.02$

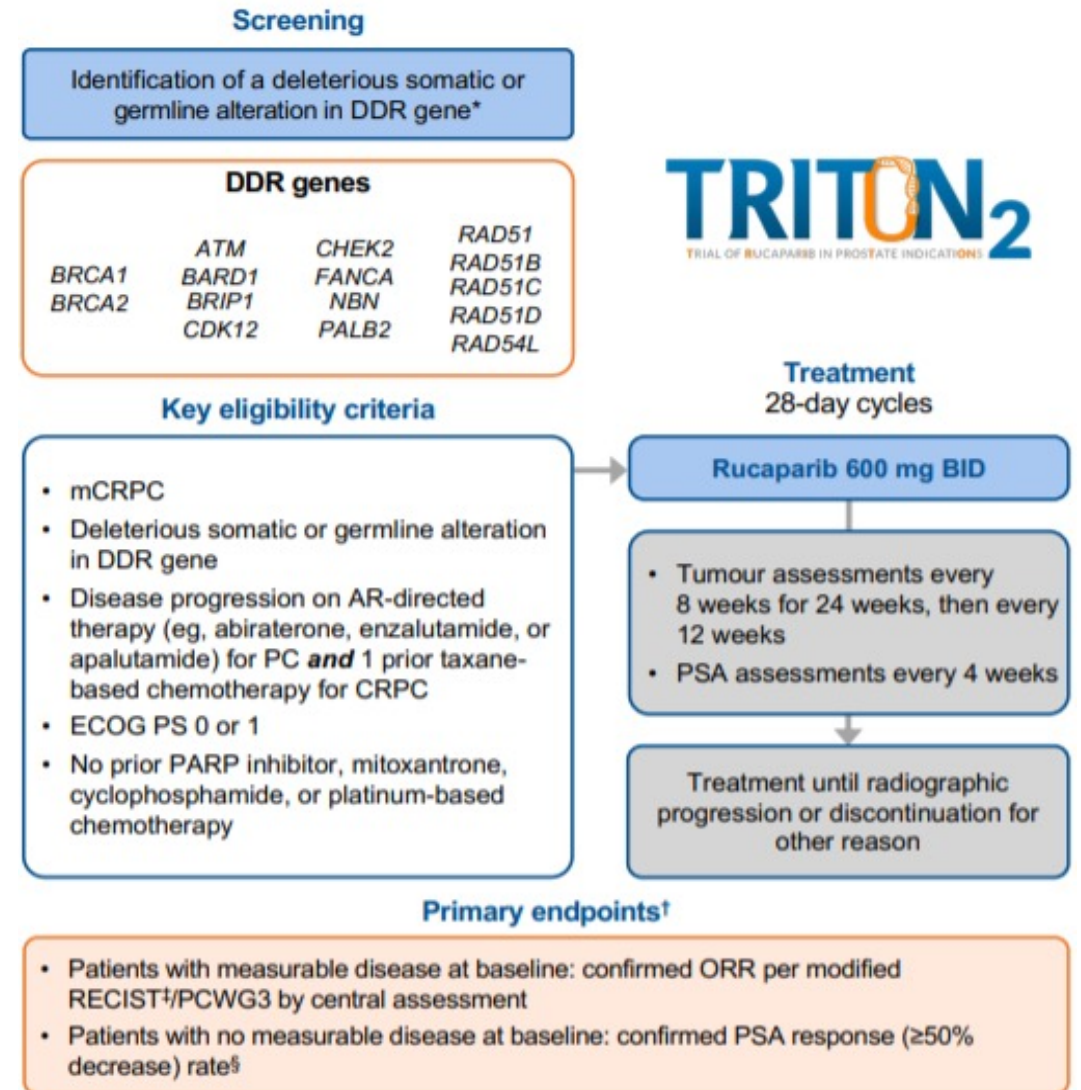


No. at Risk

Olaparib	162	158	155	152	150	147	141	136	125	115	95	86	76	67	59	50	46	33	26	17	11	4	3	2	0
Control	83	82	79	76	74	72	69	69	54	50	44	40	34	29	25	23	18	15	11	9	6	3	1	1	0

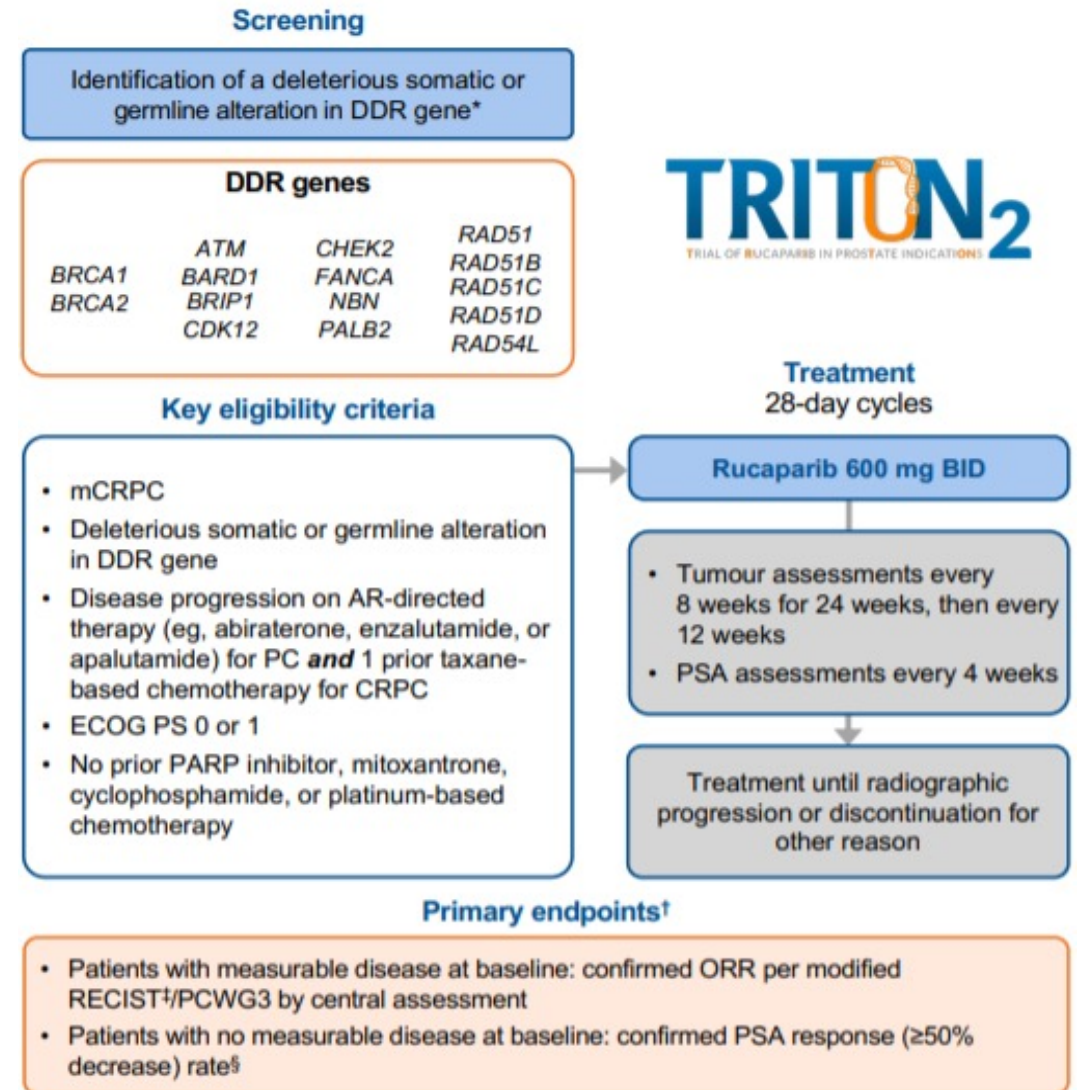
Phase II TRITON2: Rucaparib in mCRPC

- Phase 2 study rucaparib 600 mg BID
- mCRPC and a deleterious somatic or germline alteration in *BRCA1*, *BRCA2*, *ATM*, *CDK12*, or other prespecified DDR gene
- Patients have progressed on 1–2 lines of androgen receptor–directed therapy and 1 line of taxane-based chemotherapy for mCRPC



Phase II TRITON2: Rucaparib in mCRPC

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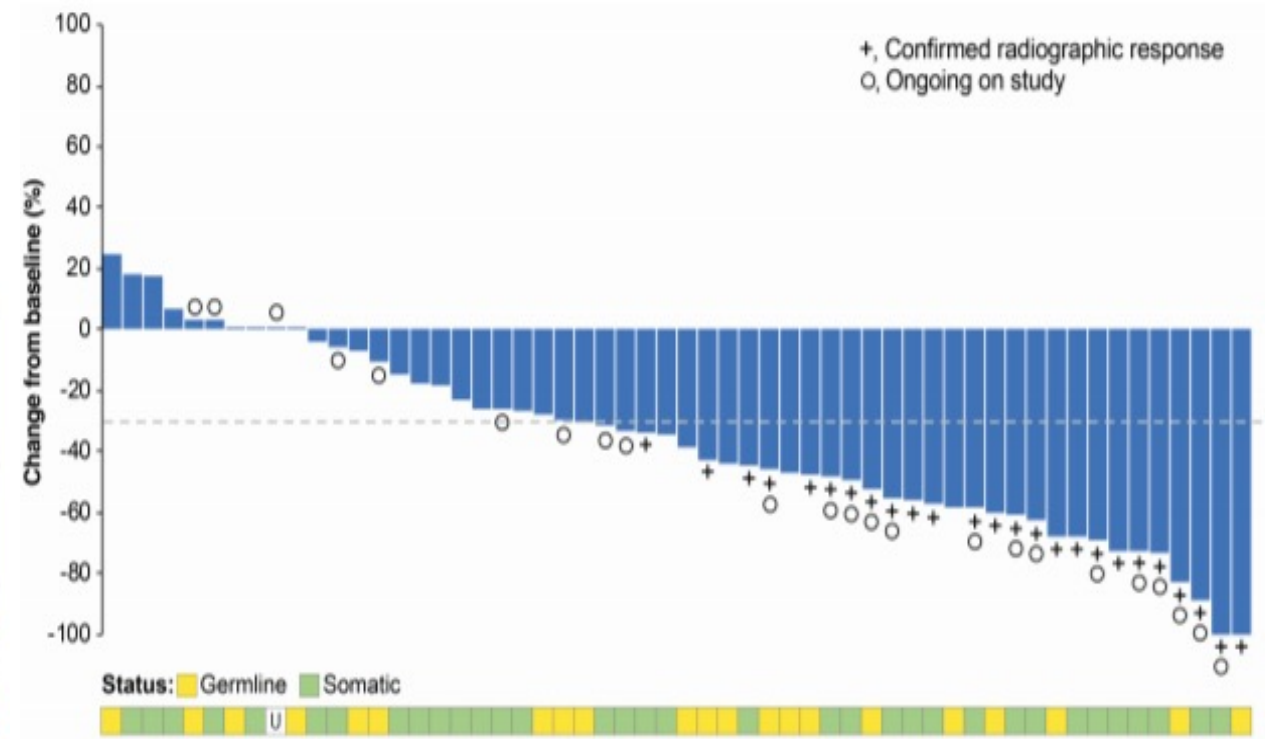
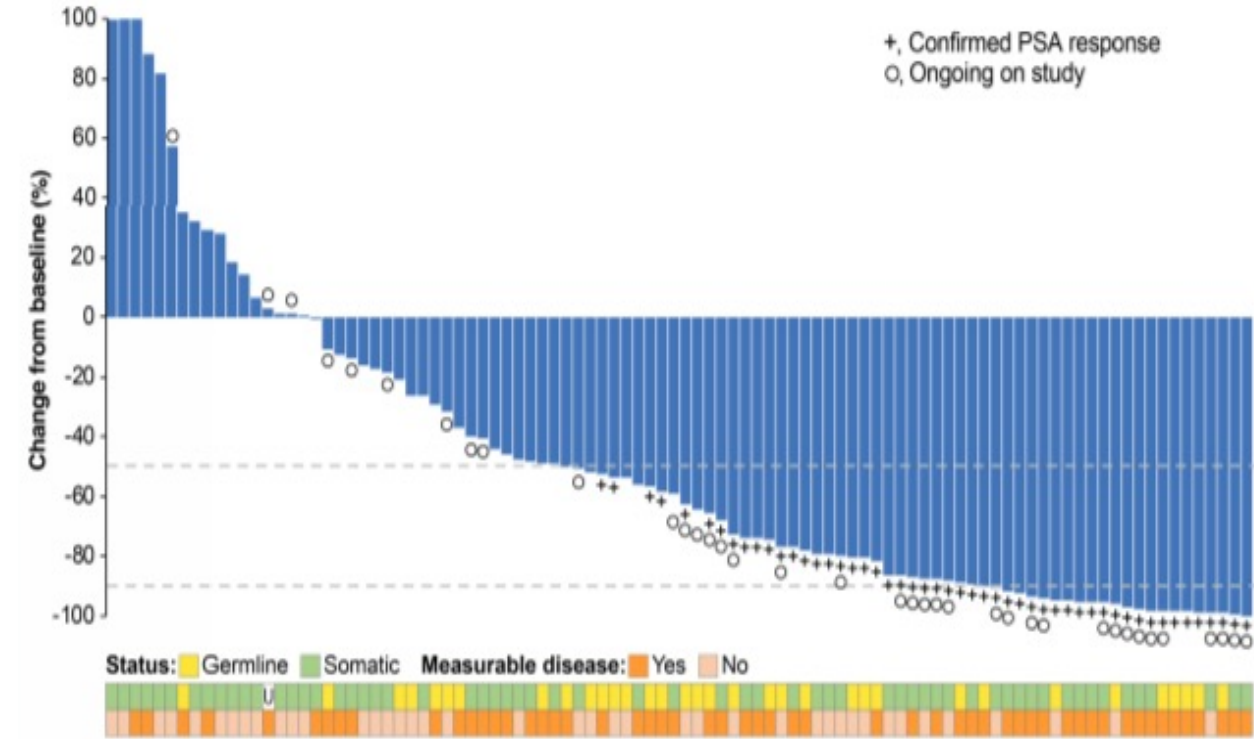
Phase II TRITON2: Rucaparib in mCRPC

**Best Change from Baseline PSA
Rucaparib-Treated Patients with a
Alteration (n=96)**

**in
*BRCA1/2***

**Best Change from Baseline in Sum of Target Lesion in
Rucaparib-Treated Patients with a
Alteration (n=56)**

BRCA1/2



Both PARP Inhibitor Approvals Within Days of Each Other—May 2020

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FDA Approves Rucaparib for Adult Patients with BRCA+ mCRPC

May 15, 2020
Hannah Slater



RELEVANT TOPICS ▾

The FDA approved rucaparib for the treatment of adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer.

The FDA approved rucaparib (Rubraca) for the treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

This indication was approved under accelerated approval based on the objective response rate (ORR) and duration of response (DOR) data observed in the multi-center, single arm TRITON2 clinical trial.

“Standard treatment options for men with mCRPC have been limited to androgen receptor-targeting therapies, taxane

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FDA Approves Olaparib for mCRPC Subset

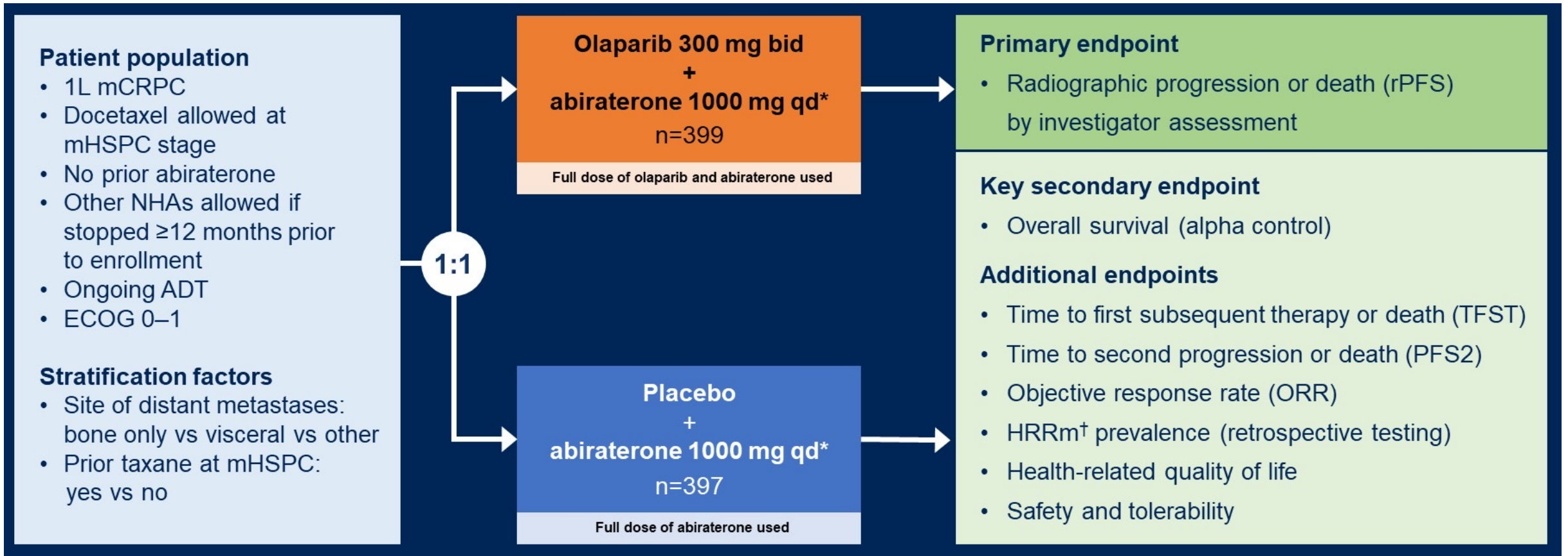
JASON M. BRODERICK @jasoncology
Tuesday, May 19, 2020



The FDA has approved olaparib (Lynparza) for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga).

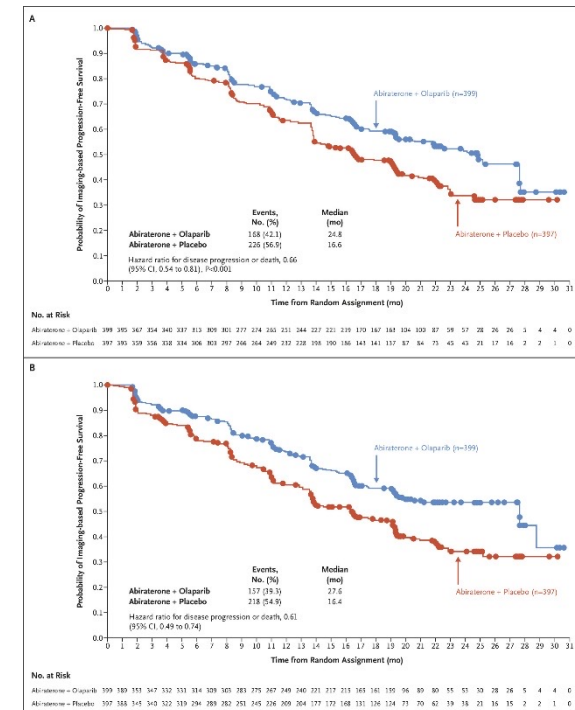
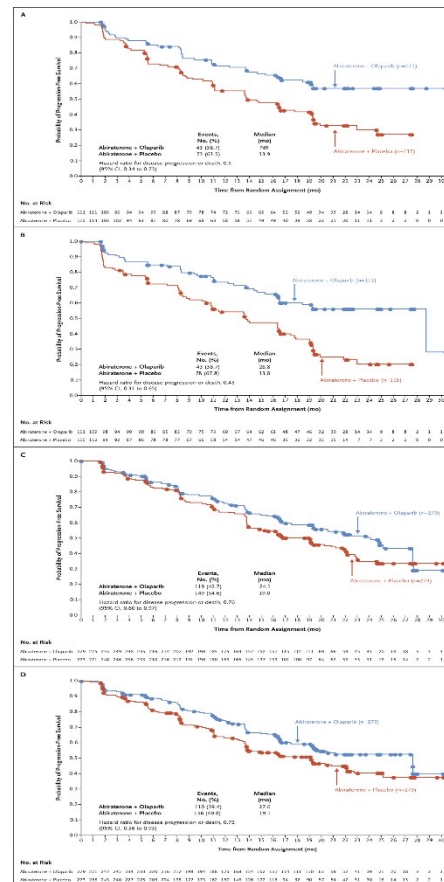
PROPEL STUDY

Clarke NW, et al NEJM Evidence 2022



All PFS analyses favored abi+Olaparib, HRR mutation HR=0.5, non HRR mutation HR=0.76

- Median PFS abi +Olaparib was 24 months and 16.8 months with abiraterone and prednisone.
- OS no difference but not mature as yet.
- Measurable disease RR increased to 58% in combination and 48% in abi arm
- PSA response rate 69% with abi alone and 79% with abi + Olaparib.

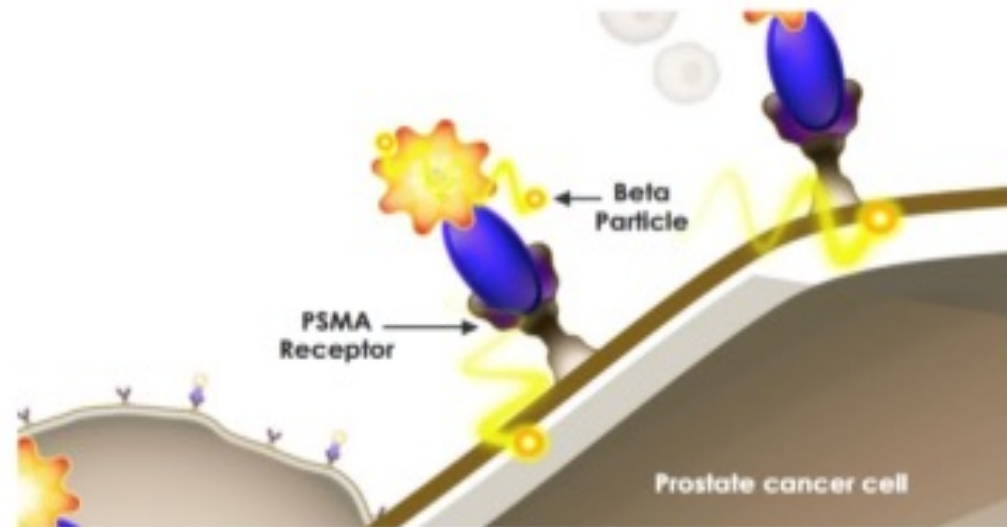


Efficacy of radioligands in mCRPC

^{177}Lu -PSMA uses a small molecule ligand to target a radioactive atom to PSMA expressing cancer cells

Delivers DNA-damaging radiation directly to the site of disease

^{177}Lu -PSMA conjugated molecule which pairs a PSMA targeting ligand to a radioactive atom ($^{177}\text{Lutetium}$).



The targeting ligand binds to PSMA which is expressed at significantly higher levels on diseased cells than on healthy tissue. Once bound to the diseased cell, the $^{177}\text{Lutetium}$ atom releases an energetic beta particle that results in lethal radiation killing the cancer cell.

Benefits of Lutetium for Therapeutic Use

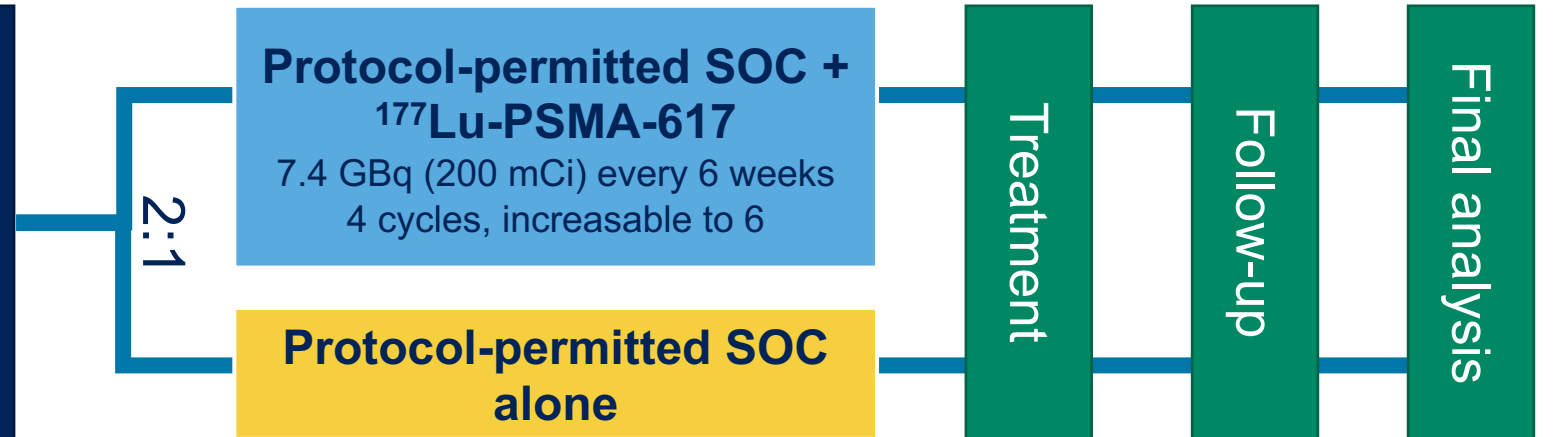
- 6.6 day half life
- <2 mm effective path length



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

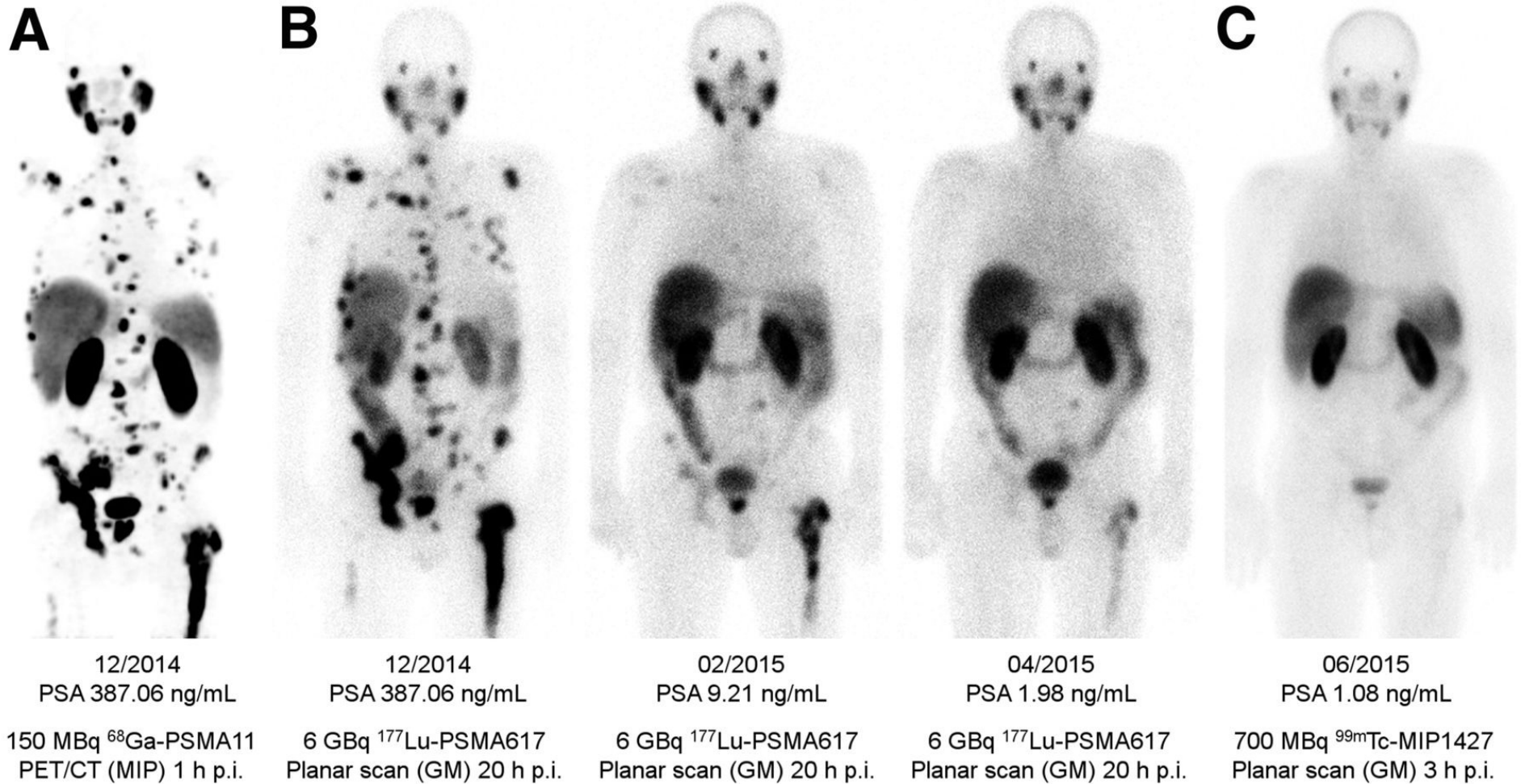
Eligible patients

- Previous treatment with both
 - ≥ 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

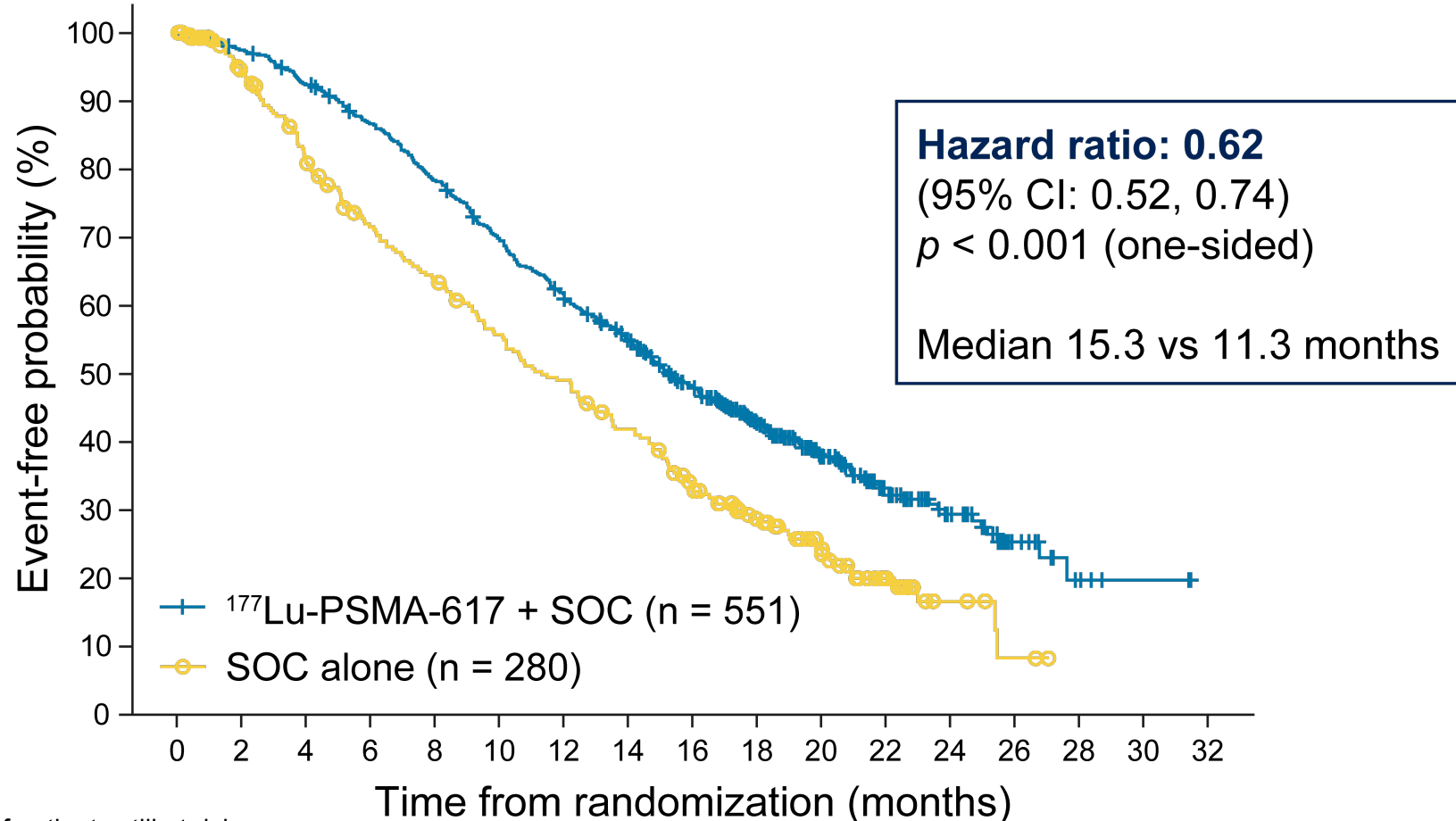
PSMA-Lu Response



Primary endpoints: ¹⁷⁷Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)



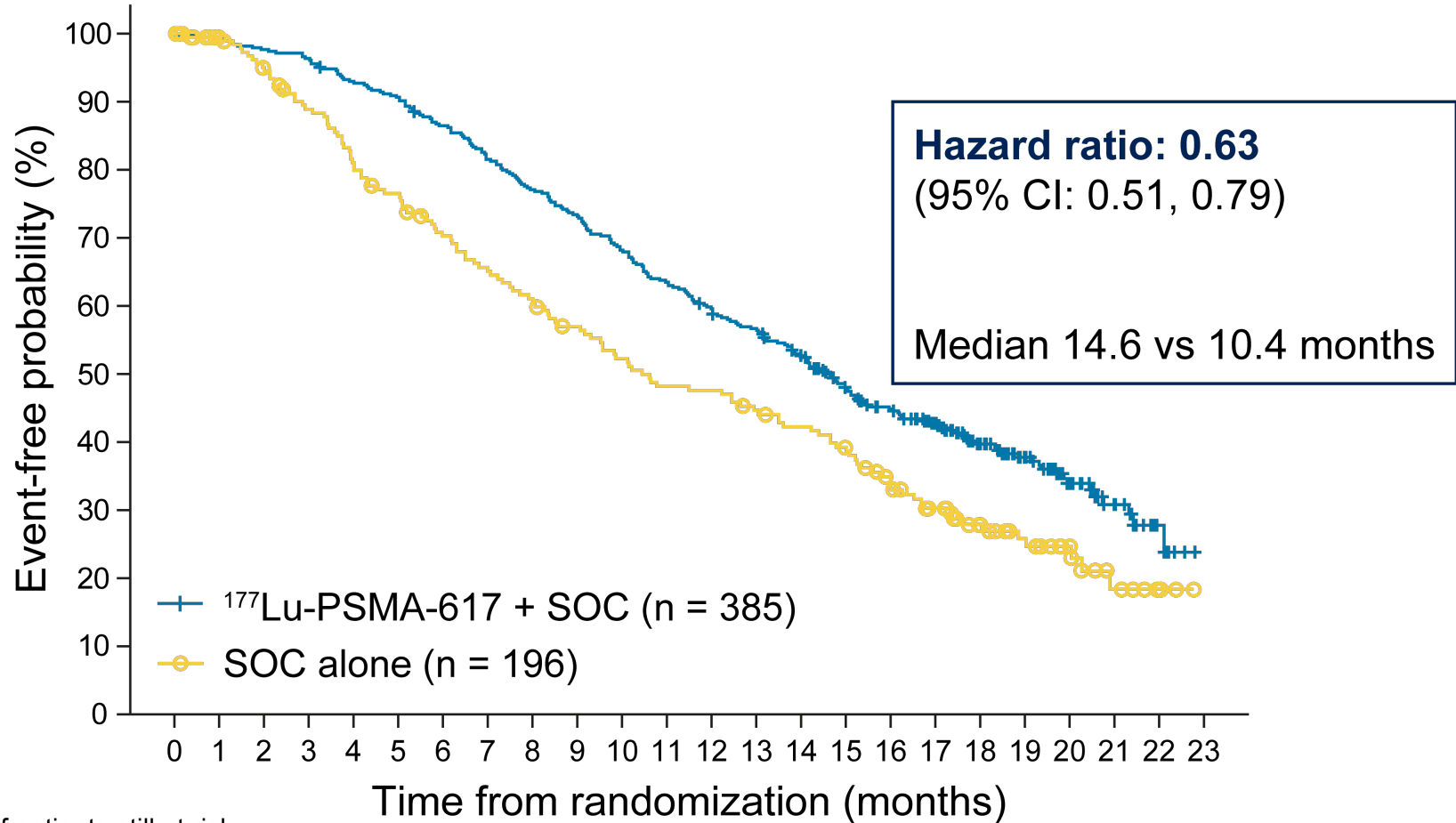
Number of patients still at risk

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

¹⁷⁷Lu-PSMA-617 prolonged OS in the rPFS analysis set

Additional analysis

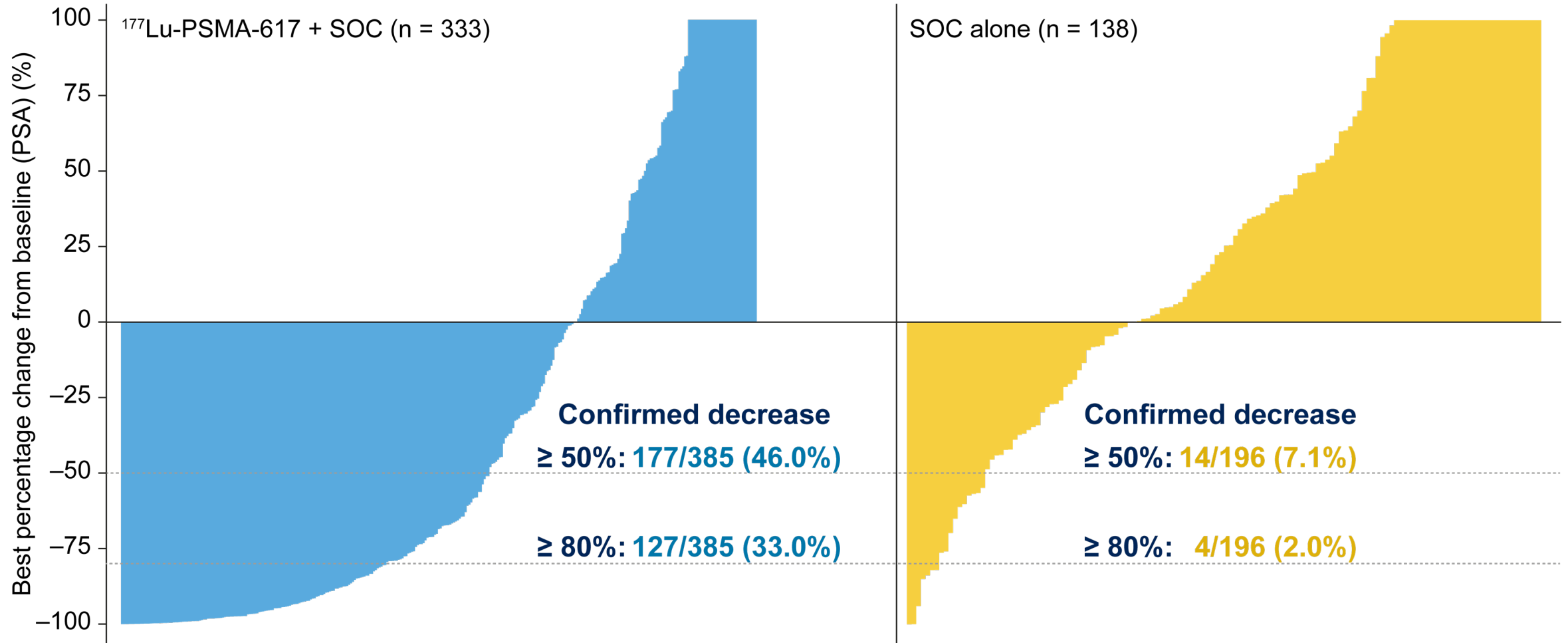
rPFS analysis set
(n = 581)



Number of patients still at risk

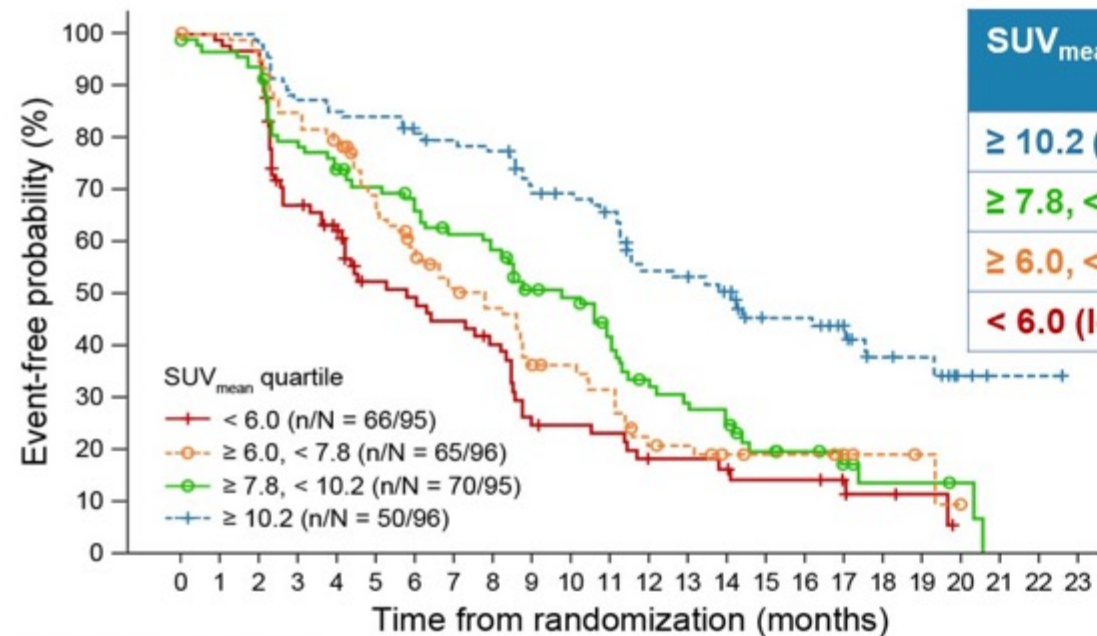
¹⁷⁷ Lu-PSMA-617 + SOC	385	382	376	371	357	348	331	312	295	281	261	243	227	215	196	169	151	128	89	68	44	24	7	0
SOC alone	196	181	171	158	144	135	122	113	106	97	89	82	81	75	70	64	51	42	30	23	15	7	3	0

Secondary endpoint: PSA responses favored the ^{177}Lu -PSMA-617 arm among evaluable patients



SUV mean correlated with rPFS

- Higher whole-body SUV_{mean} was associated with prolonged rPFS



SUV _{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

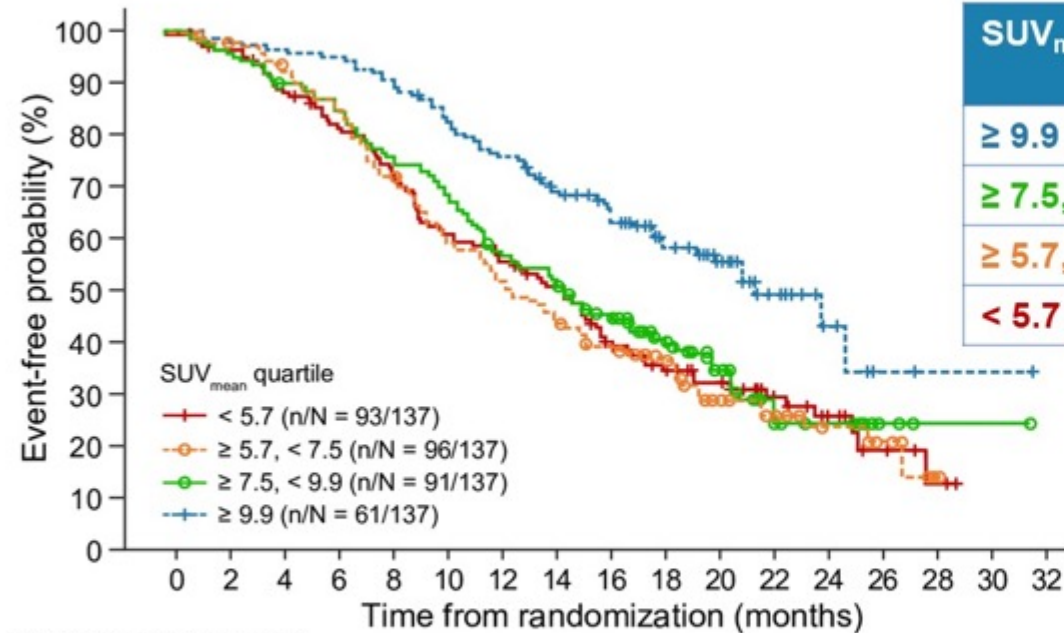
Number of patients still at risk

≥ 10.2	96	95	94	82	80	79	74	72	70	61	58	54	41	40	36	25	25	19	11	10	3	1	1	0
≥ 7.8, < 10.2	95	90	87	73	69	63	60	53	51	41	39	31	23	20	17	11	9	6	4	4	2	0	0	0
≥ 6.0, < 7.8	96	94	91	79	72	57	47	38	34	26	24	21	13	12	9	8	8	7	3	2	1	0	0	0
< 6.0	95	91	87	56	50	35	33	30	26	17	15	14	10	10	9	7	7	5	3	2	0	0	0	0

SUV _{mean}	rPFS HR [95% CI], p value
Univariate analysis	0.88 [0.84, 0.91], < 0.001
Multivariate analysis	0.86 [0.82, 0.90], < 0.001

PSMA scan SUV mean correlated with OS

- Higher whole-body SUV_{mean} was associated with improved OS



SUV _{mean} quartile	Median OS (months)
≥ 9.9 (highest)	21.4
≥ 7.5, < 9.9	14.6
≥ 5.7, < 7.5	12.6
< 5.7 (lowest)	14.5

Number of patients still at risk

≥ 9.9	137	135	132	130	124	116	104	91	79	56	37	17	6	2	1	1	0
≥ 7.5, < 9.9	137	133	123	118	104	95	79	71	57	41	28	13	8	3	1	1	0
≥ 5.7, < 7.5	137	134	128	112	97	82	71	61	50	34	20	15	10	5	1	0	0
< 5.7	137	130	121	108	98	82	76	64	48	34	27	18	12	5	2	0	0

SUV _{mean}	OS HR [95% CI], p value
Univariate analysis	0.92 [0.89, 0.95], < 0.001
Multivariate analysis	0.88 [0.84, 0.91], < 0.001

VISION Trial Results: Vaishampayan et al. ASCO 2022

Eligible patients

- Previous treatment with **both**:
 - ≥ 1 ARPI, and
 - 1–2 taxane regimens
- Protocol-permitted SoC planned before randomization
 - Excluding chemotherapy, immunotherapy, radium-223, or other investigational drugs
- ECOG PS 0–2
- Life expectancy > 6 months
- Meet trial-specific criteria on baseline [^{68}Ga]Ga-PSMA-11^a PET/CT

2:1

Protocol-permitted SoC +
 ^{177}Lu -PSMA-617 (n = 551)
7.4 GBq (200 mCi)
every 6 weeks
up to 6 cycles

Protocol-permitted SoC
(n = 280)

Key outcomes

^{177}Lu -PSMA-617 prolonged OS and improved rPFS

rPFS^b
HR 0.40

99.2% CI: 0.29, 0.57;
 $p < 0.001$

Median:
8.7 vs 3.4 months

OS^c
HR 0.62

95% CI: 0.52, 0.74;
 $p < 0.001$

Median:
15.3 vs 11.3 months

VISION study conclusions

- Adding ^{177}Lu -PSMA-617 to safely combinable standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
 - Extended overall survival
 - Delayed radiographic disease progression
- ^{177}Lu -PSMA-617 was well tolerated
- These findings warrant adoption of ^{177}Lu -PSMA-617 as a new treatment option in patients with mCRPC

NOVEL AGENTS

AR degraders

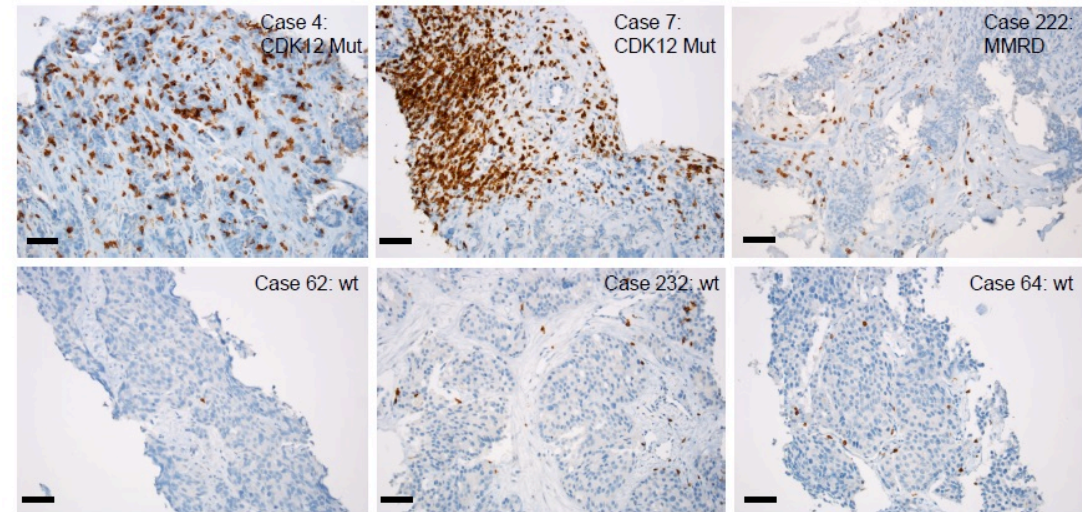
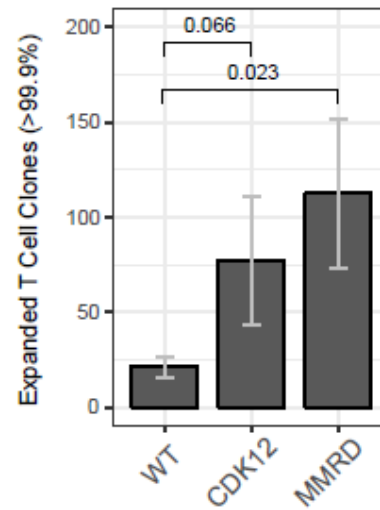
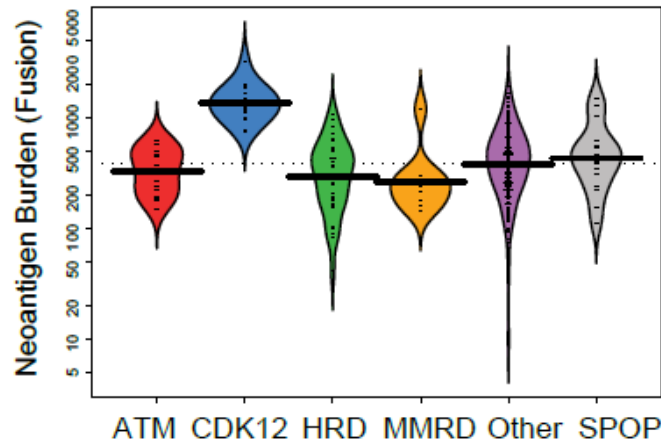
Oral chemo

T cell based Immune Therapy

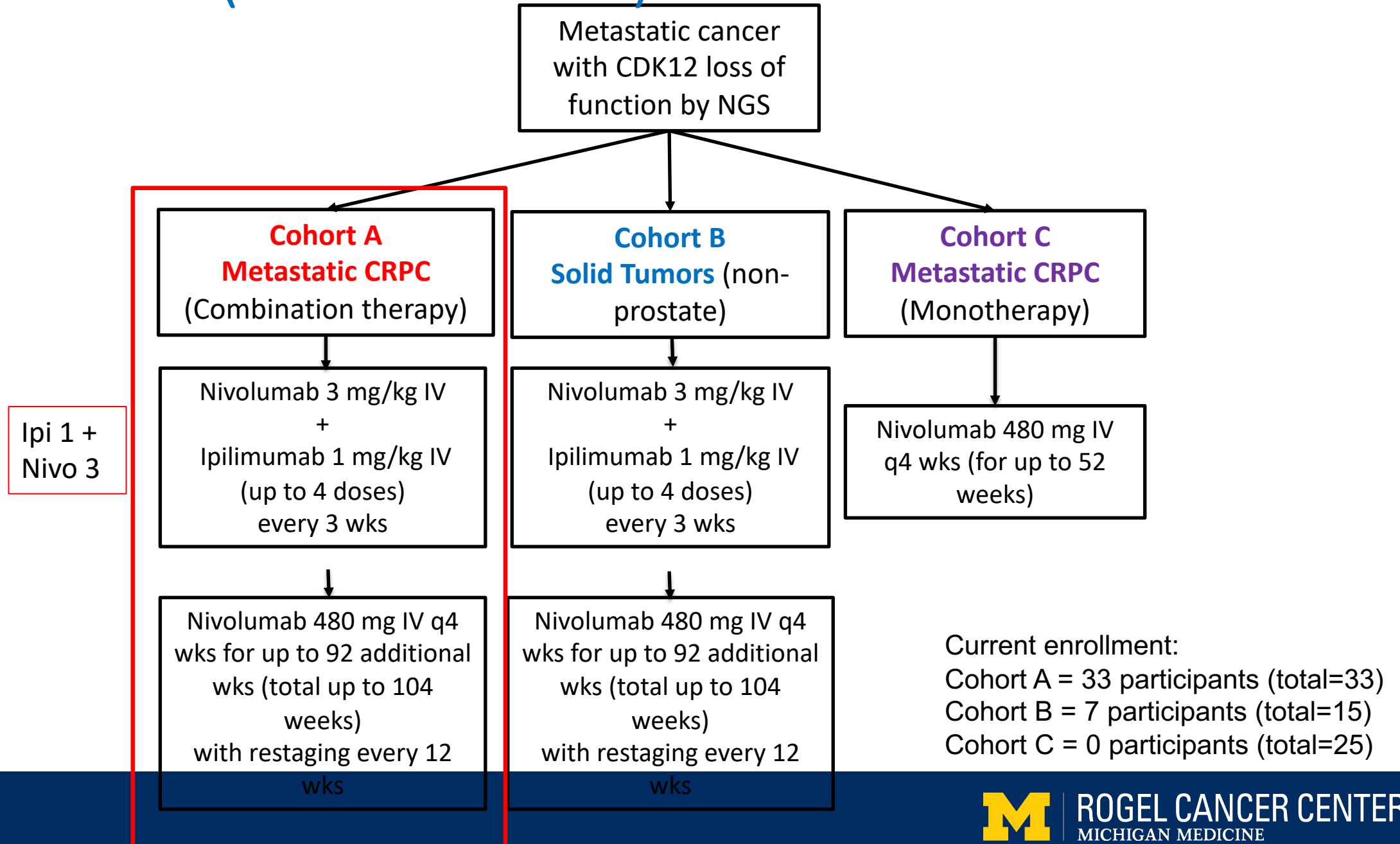
Neuroendocrine Disease

CDK12 Loss Prostate Cancer

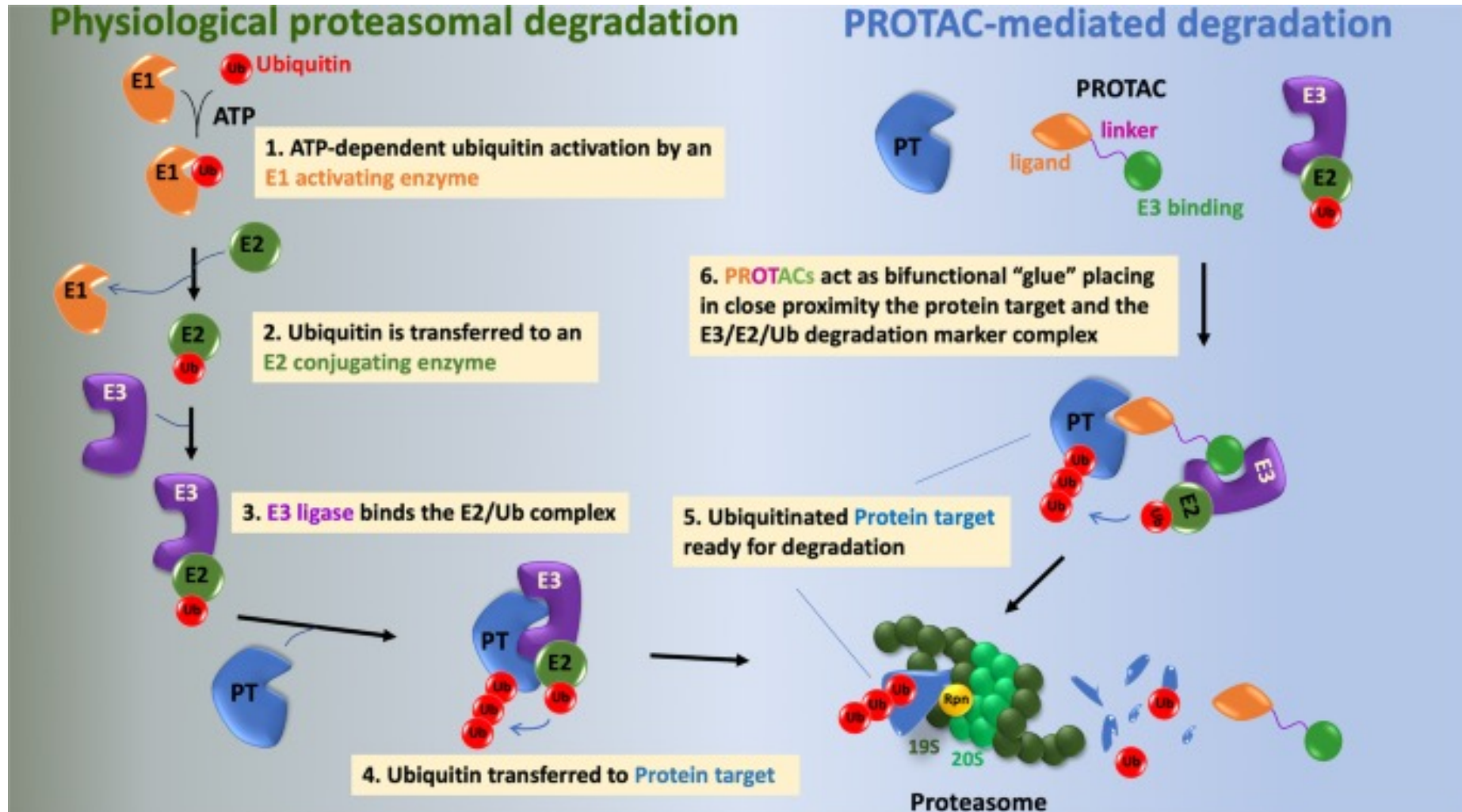
- *CDK12*-mutant subtype displays elevated neoantigen burden from gene fusions
- Mirrored by increased T cell infiltration and clonal expansion



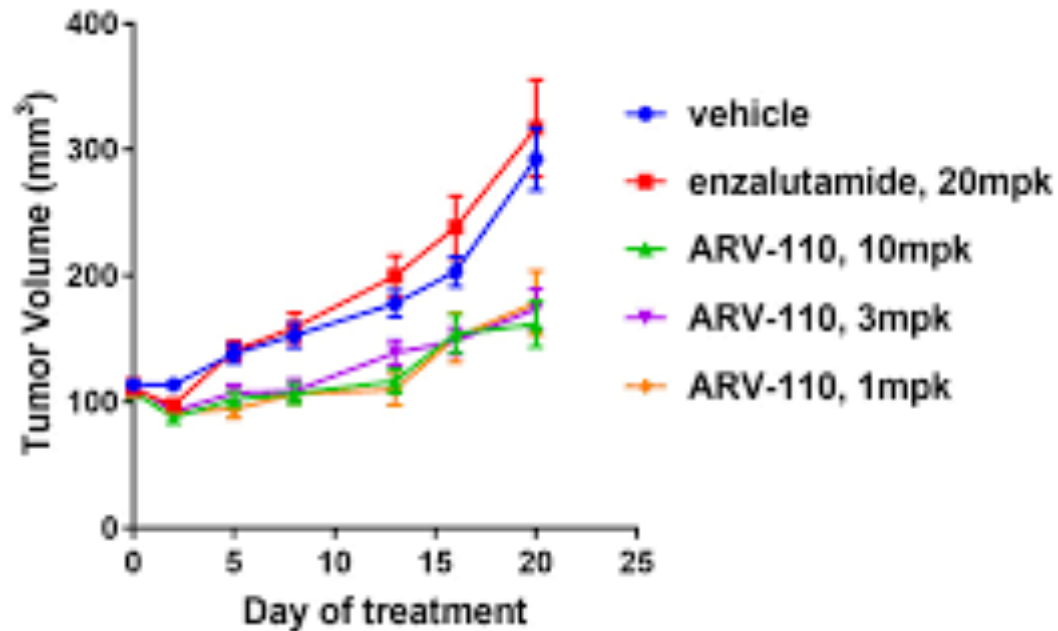
IMPACT (UMCC 2018.050) Schema NCT03570619



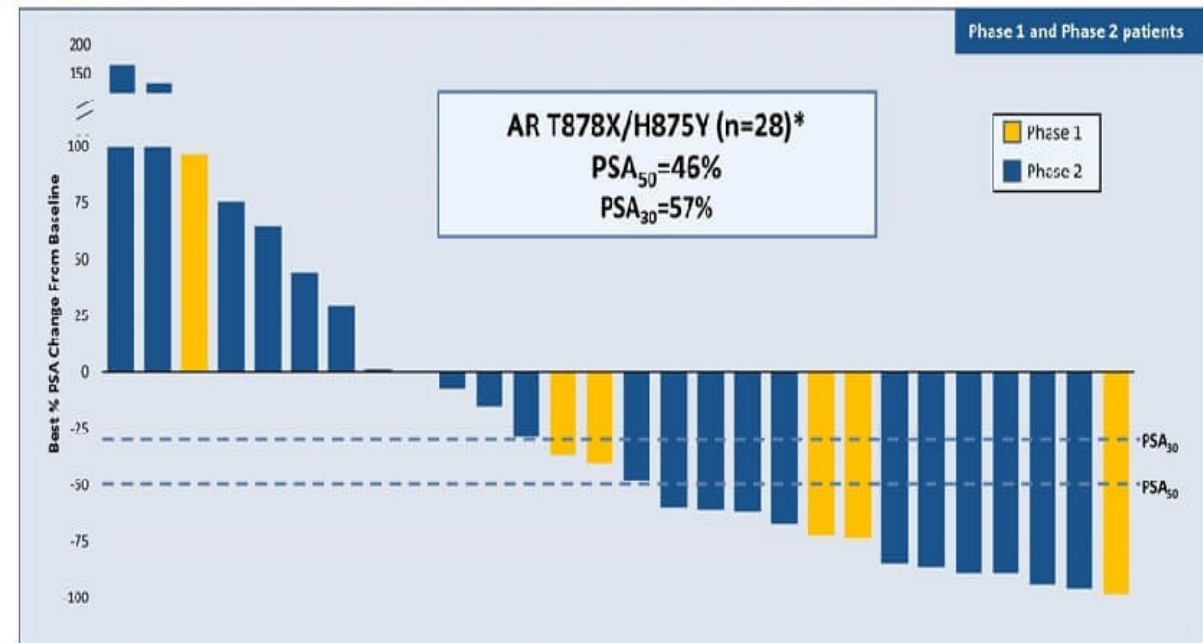
AR Degraders : Protein lysing chimera



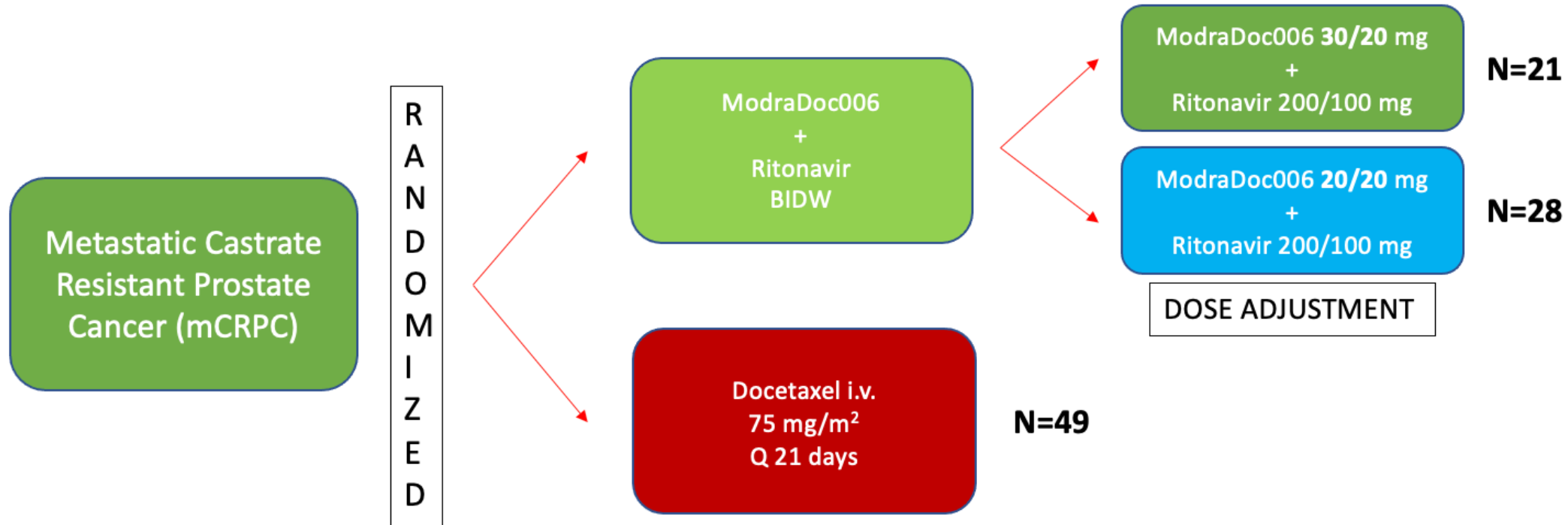
Promising Responses in Enza Resistant mCRPC: Petrylak DP et al GU ASCO 2020 and 2022



46% PSA₅₀ in all patients with AR T878X/H875Y tumor mutations in Ph 1 and across all ARDENT subgroups supports the potential for accelerated approval



M18MDP: Multicenter phase IIb study to evaluate the efficacy and tolerability of ModraDoc006 in combination with ritonavir (denoted ModraDoc006/r) in patients with metastatic castration-resistant prostate cancer, suitable for treatment with a taxane: Vaishampayan U et al. ASCO 2022



- Primary endpoint: rPFS
- Secondary: PSA RR, PFS@6m, TTP, DOR, PSA PFS, TT I stSkEv, ORR
- PI: Ulka Vaishampayan, University of Michigan

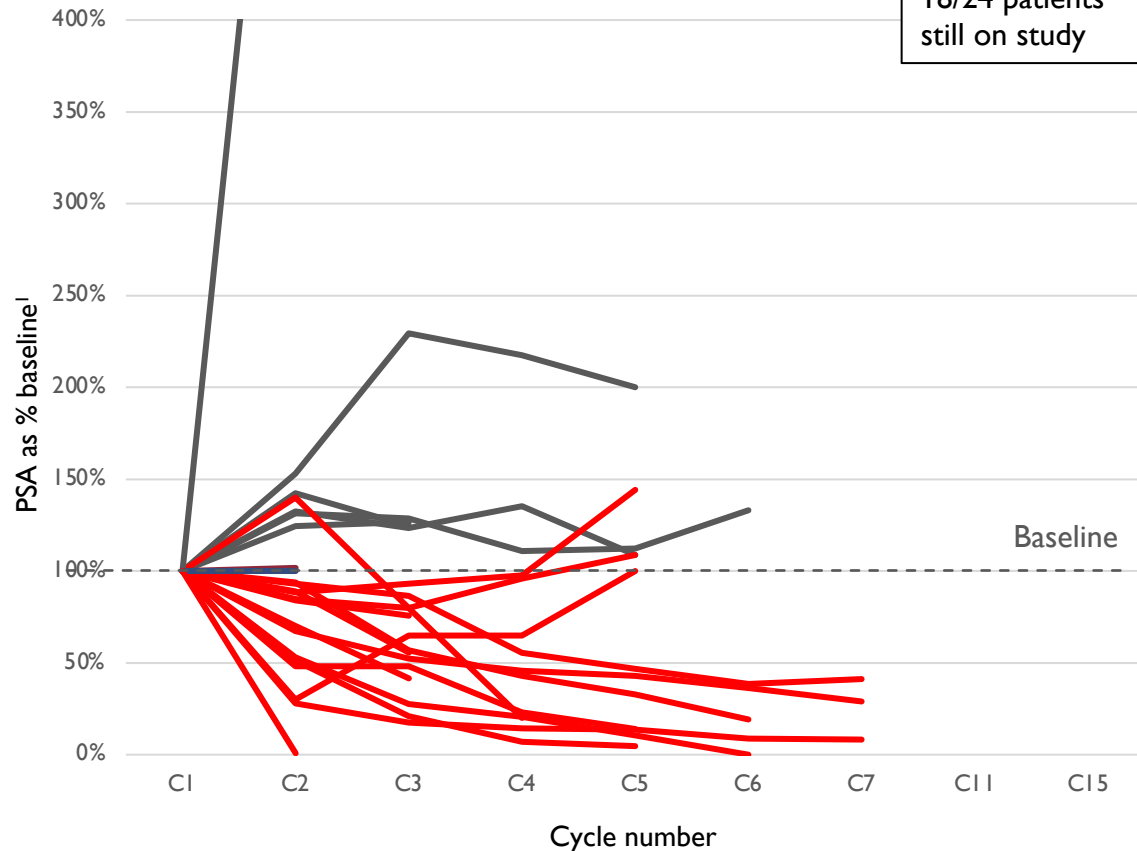
Preliminary data

Preliminary Activity Data

Both IV & ModraDoc006/r show clear impact on PSA levels – rPFS data not yet available, and majority of patients still on treatment

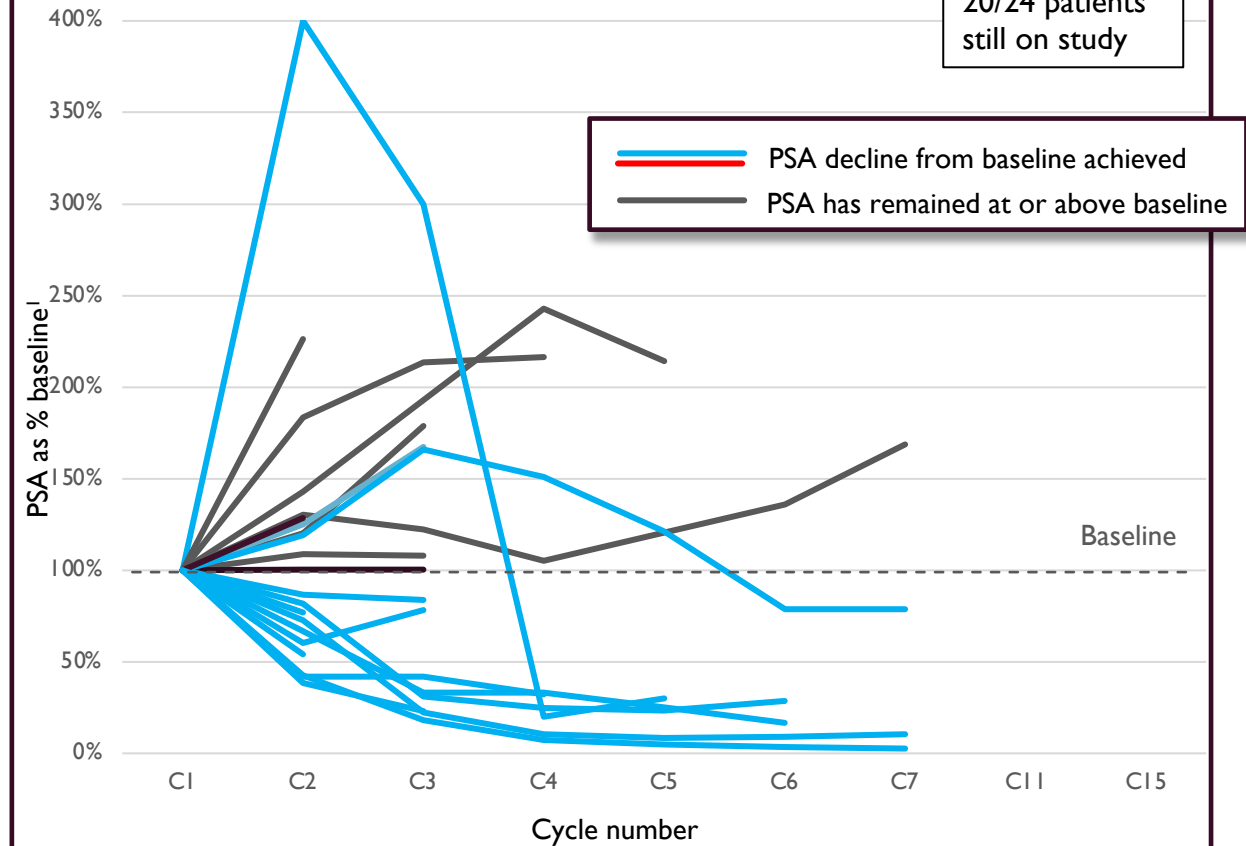
IV docetaxel
under protocol v3

18/24 patients
still on study



ModraDoc006/r, 20-20/200-100 dose
under protocol v3

20/24 patients
still on study



1. For patients with missing data, average of prior and subsequent measurement taken ((2 patients in IV, 1 patient in ModraDoc006/r arms).

❖ ModraDoc006/r

Convenient oral
weekly dosing

Favorable safety profile
as compared to IV
docetaxel

Clinical Efficacy Noted

Efficacy

- Preliminary efficacy noted (> 50% of all patients ongoing)
- Responses improve over longer treatment period
- Encouraging signs of response for ModraDoc006/r

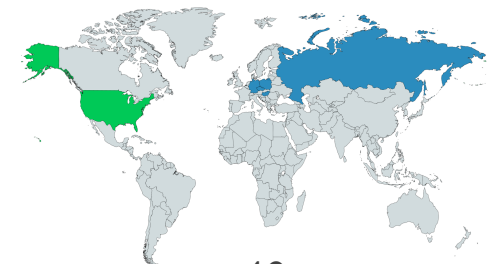
CONCLUSION

Safety

ModraDoc006/r typically exhibits mild GI-toxicities

- No hematological toxicity at the 20-20/200-100 dose
- Elimination of infusion reactions
- Improved safety profile as compared to IV docetaxel with reduced cytopenias, infections and neuropathy.

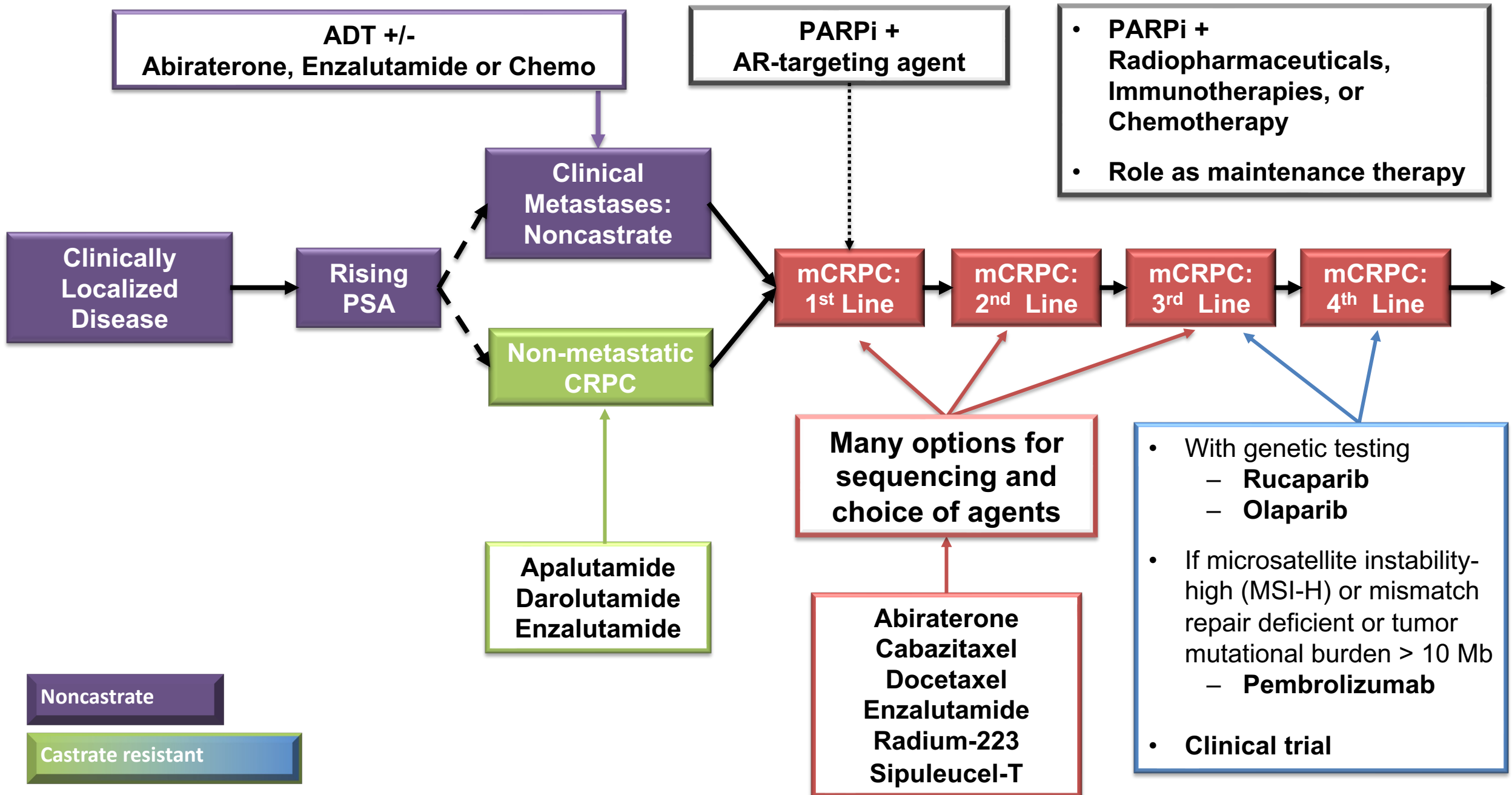
Acknowledgement: We express our sincere gratitude to the patients, their families and all the faculty and staff at the global centers that participated in the study.



Lenvatinib + Pembrolizumab in Neuroendocrine Prostate Cancer: A Hoosier Cancer Research Network Study

PI: Ulka Vaishampayan MD

- Lenvatinib and pembrolizumab combination has established preclinical synergy: In syngeneic CT26 CRC and Hepa1-6 HCC murine tumor models, the combination of lenvatinib and an anti-PD-1 antibody produced greater reduction in tumor volume and a higher response rate than either agent alone, including complete regression of tumors in some animals
- The combination showed immunomodulatory properties: increased tumor infiltration of effector CD8+ T cells and decreased monocytes and macrophages.
- Clinical safety and efficacy of combination is established
- Combination has proven clinical efficacy in endometrial cancer and is FDA approved.
- We are conducting a phase II trial in mCRPC with neuroendocrine features or in small cell ca prostate.



Conclusions

- Careful pt selection is required for nmCRPC especially as treatment commitment is for prolonged periods of time in an asymptomatic patient population
- 2 Androgen receptor targeted agents were not better than 1; Alliance trial showed no benefit for combo of abi+enza vs enza alone.
- Cardiac risks , falls, fractures and other comorbidities should be considered.
- mHSPC: Critical discussion of pros and cons of docetaxel chemo vs ARAT.
- Biomarker exploration is needed to help guide the type of therapy.
- Almost all pts with mCRPC space will be pretreated with ARAT agent. This will impact therapy choices and sequencing in mCRPC.
- Genomic testing and actionable mutations should be evaluated
- PARP inhibitor maybe used in combo with abiraterone in mCRPC

Facts about
PROSTATE CANCER

THE PROSTATE IS A SMALL, WALNUT-SHAPED GLAND FOUND ONLY IN MALES. IT CONTAINS CELLS THAT MAKE FLUID (SEMEN) TO PROTECT AND NOURISH SPERM

NEARLY **3 MILLION** MEN IN THE UNITED STATES ARE PROSTATE CANCER SURVIVORS

IN ITS EARLY STAGES, PROSTATE CANCER OFTEN HAS **NO SYMPTOMS**

ALTHOUGH THE **PROSTATE-SPECIFIC ANTIGEN (PSA)** BLOOD TEST IS THE MAIN SCREENING TEST FOR PROSTATE CANCER, PROSTATE CANCER CAN ONLY BE DIAGNOSED THROUGH A **BIOPSY OF THE PROSTATE**

PROSTATE CANCER IS THE **MOST COMMON** CANCER IN AMERICAN MEN

180,000 NEW CASES OF PROSTATE CANCER WILL BE DIAGNOSED THIS YEAR

MOST DOCTORS AGREE IF YOU DO THINGS THAT ARE **HEART HEALTHY**, YOU WILL ALSO KEEP YOUR PROSTATE HEALTHY

IF YOU ARE **55 TO 69** YEARS OF AGE, **TALK TO YOUR DOCTOR** ABOUT WHETHER PROSTATE SCREENING IS RIGHT FOR YOU

ASIDE FROM AGE, RISK FACTORS FOR PROSTATE CANCER INCLUDE FAMILY HISTORY AND RACE

- 1 in 7 men will be diagnosed with prostate cancer
- Your chance of being diagnosed increases to:
 - 1 in 5 if you are African-American
 - 1 in 3 if you have a family history of the disease

Urology Care FOUNDATION™
The Official Foundation of the American Urological Association

For more information about prostate cancer, visit the Urology Care Foundation's website: UrologyHealth.org

**Expert Panel - Today
Advanced Prostate Cancer**

So, gentlemen, we are all agreed, advanced prostate cancer sucks! And we're the experts so we oughta' know.

Too bad we don't have a cure or treatment up our sleeve...

And all we have to do is say that over the next 30 minutes, smile for the camera, and look really smart.



Being an expert can be really hard sometimes...

