The New and the Old in Advanced Prostate Cancer

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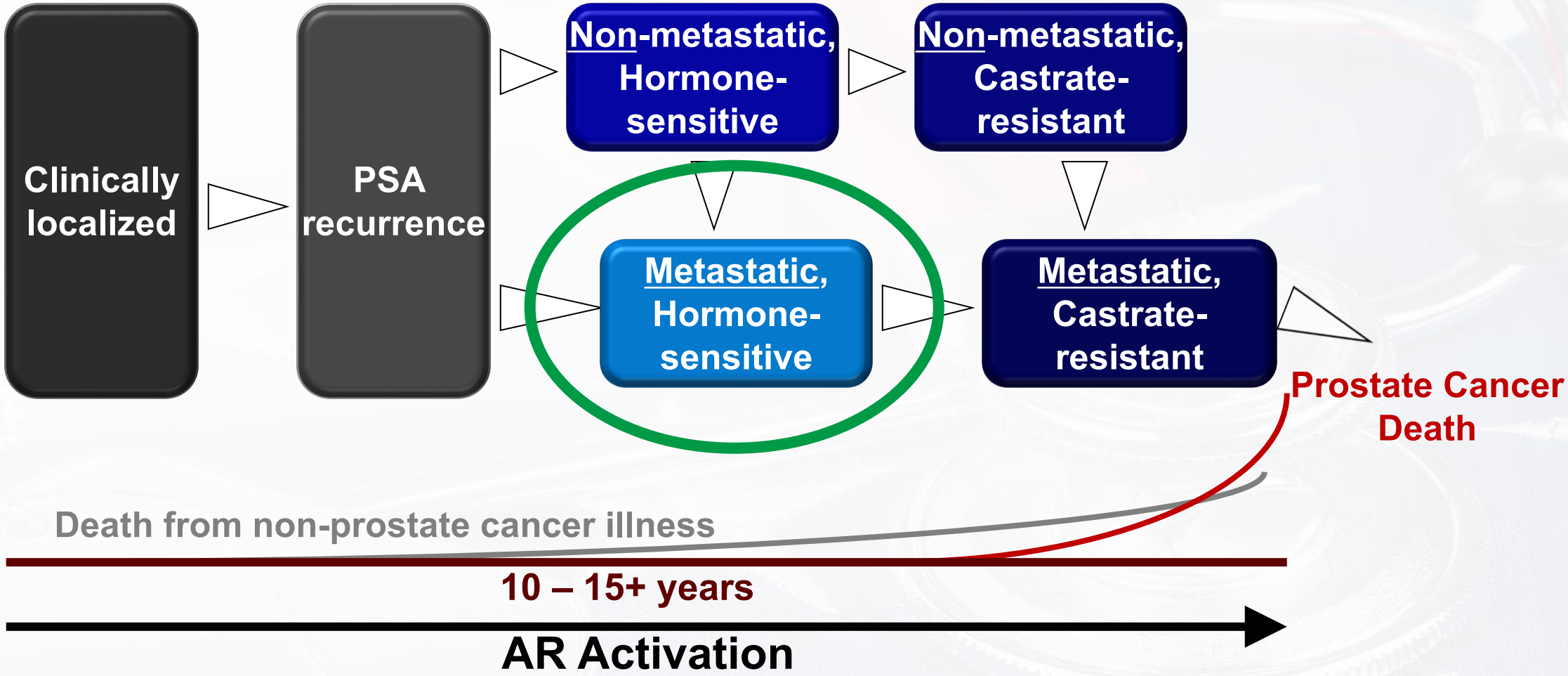
Three Main Objectives

- Management of Castrate Sensitive Prostate Cancer
- Advances in Castrate Resistant Prostate Cancer
- Novel Therapies and Advances

Clinical States of Prostate Cancer



Rettig, MB. Current Treatment Strategies for Advanced Prostate Cancer. *Federal Practitioner*. Dec 8, 2017.

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

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

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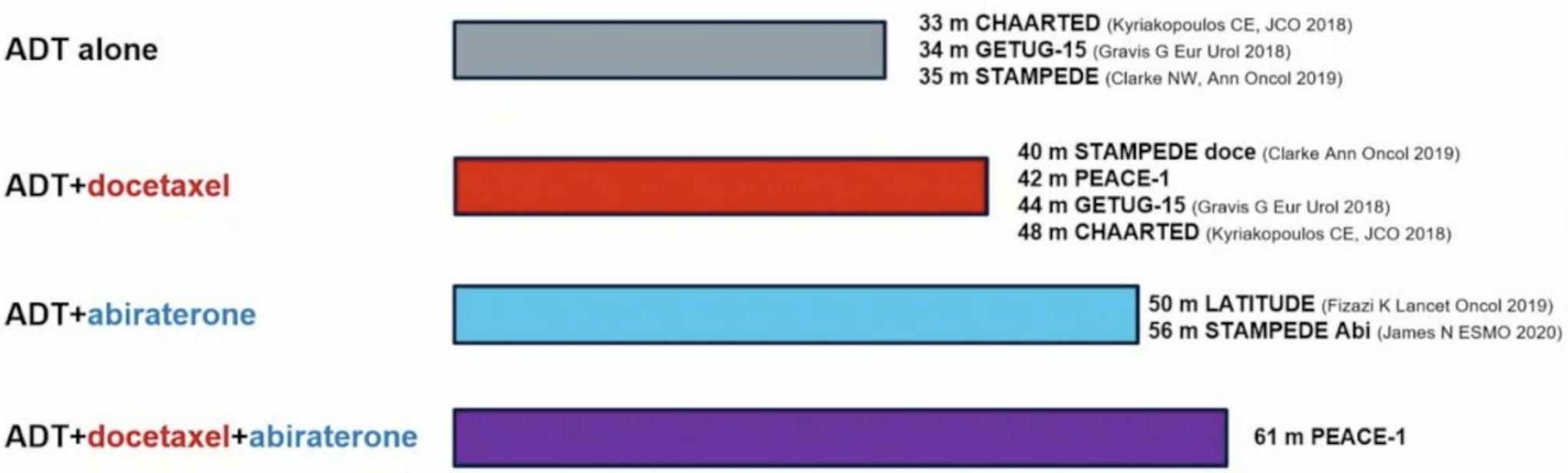
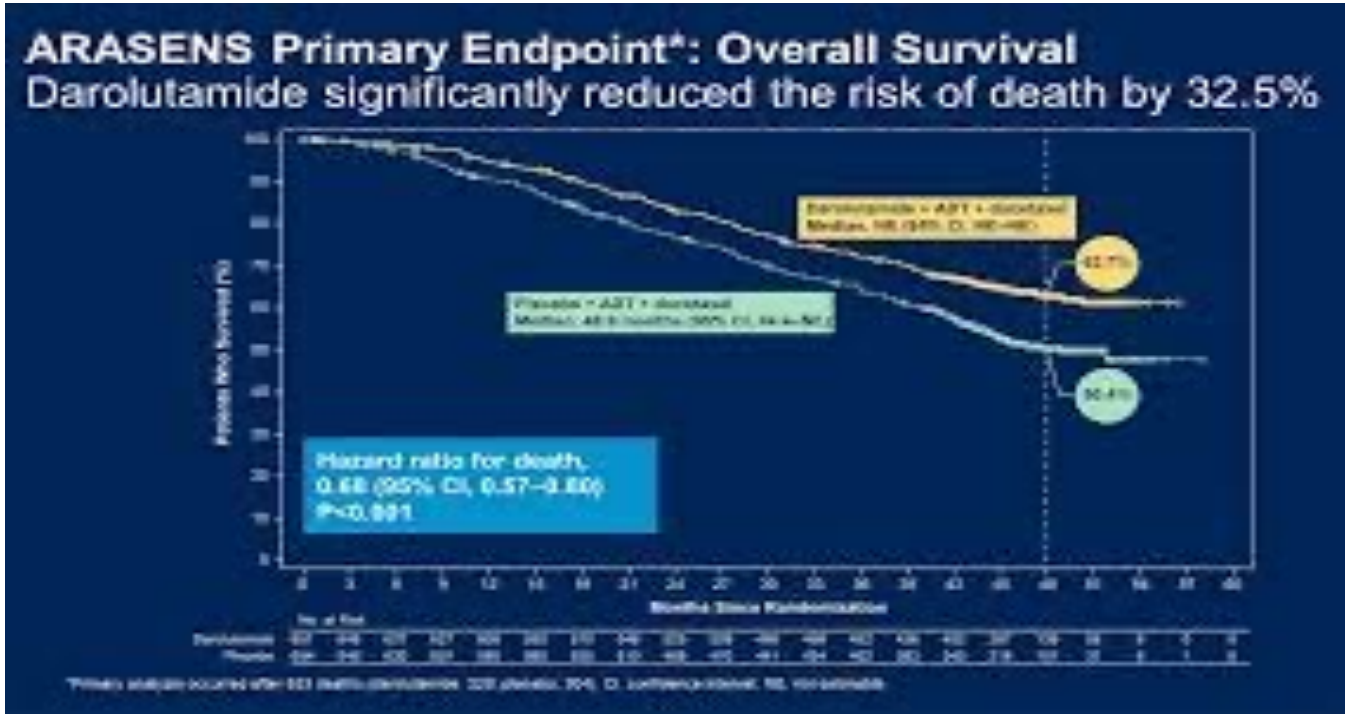
Median Overall Survival
(*de novo* High-Volume mCSPC)

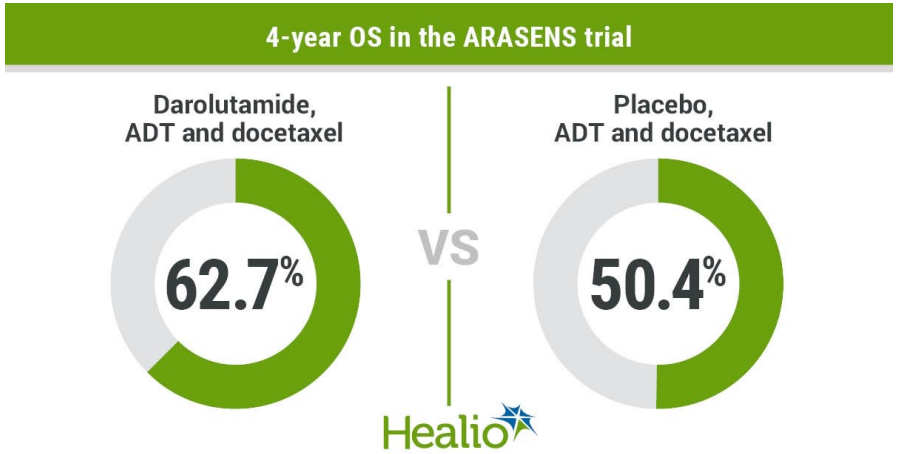


2021 ESMO congress

Karim Fizazi

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





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

METHODS

STAMPEDE

1974 M0 pts with M0 node positive or high-risk node negative PCa

Phase 3 trial

ADT +/- AAP +/- ENZ

PEACE-1

1173 pts (57% high-, 43% low-volume) with *de novo* mCSPC

Phase 3 trial

SoC (ADT with/out docetaxel) +/- AAP +/- RT

RESULTS

6-y survival improved from **77%** to **86%** in patients taking AAP-based therapy

OS improved from **4.7 yrs** (median OS) to **5.7 yrs** (median OS) in patients taking AAP (with or without RT) plus SoC

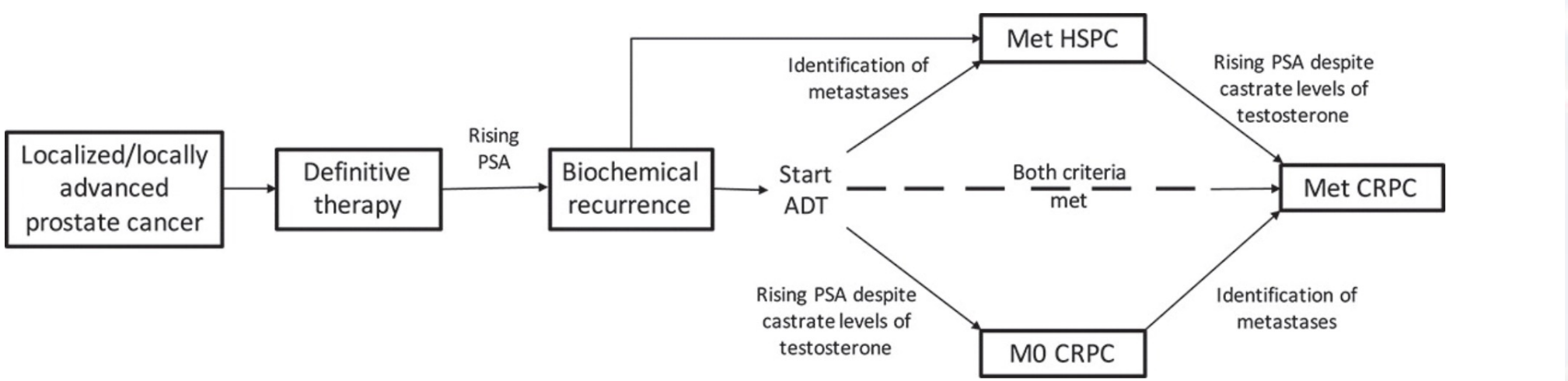
CONCLUSIONS

Addition of abiraterone acetate plus prednisolone (AAP) to standard therapy lengthened survival compared to standard therapy alone in patients with hormone/castration-sensitive 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

2021 ESMO congress

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



- Predictor of outcomes in nmCPRC[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

[1] Freeland, et al. *J Urol.* 2019;201:abstr MP34-07. [2] Fuld, et al. *J Clin Oncol.* 2018;36:suppl_abstr e17057.

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]

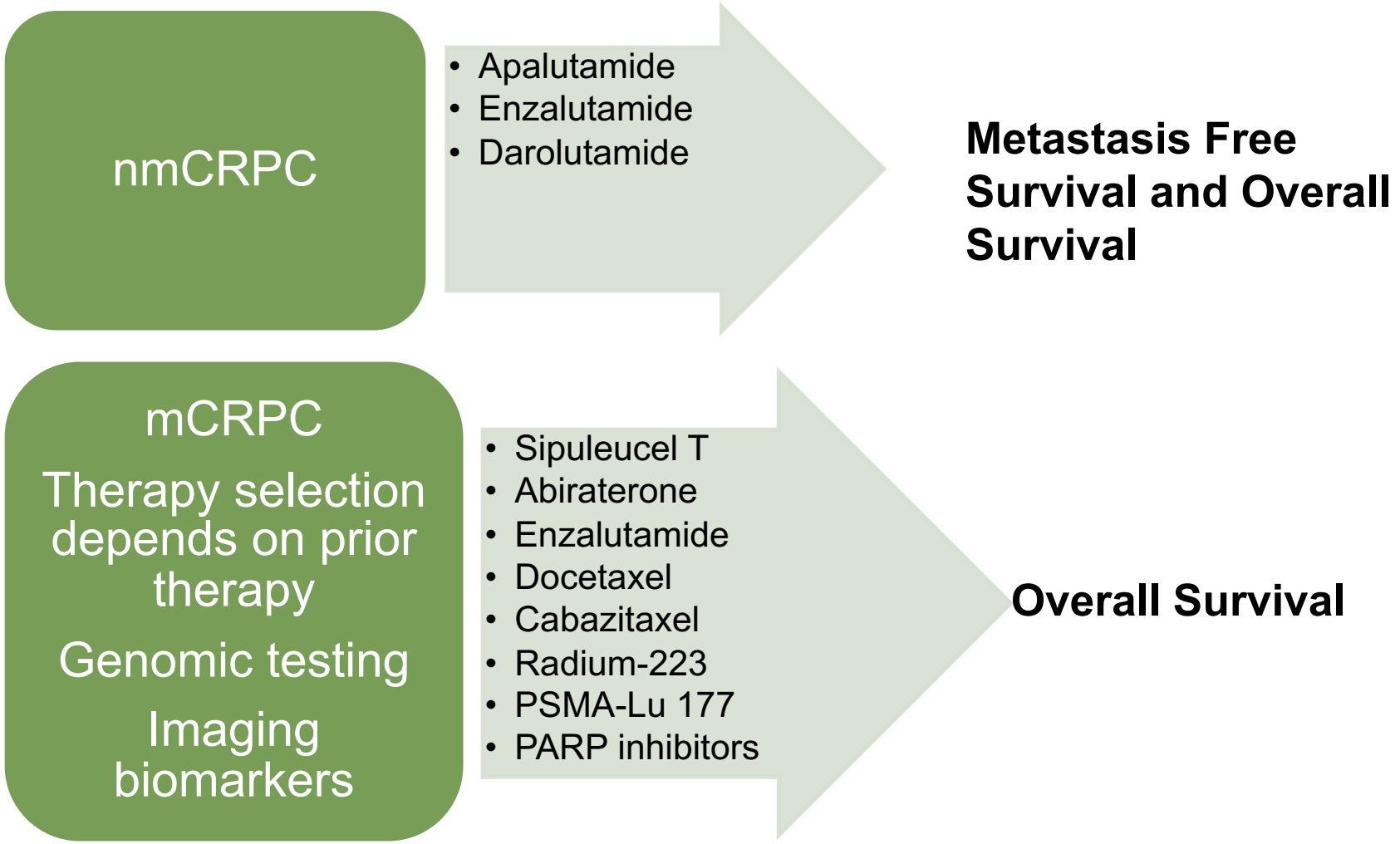
Delay disease progression

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



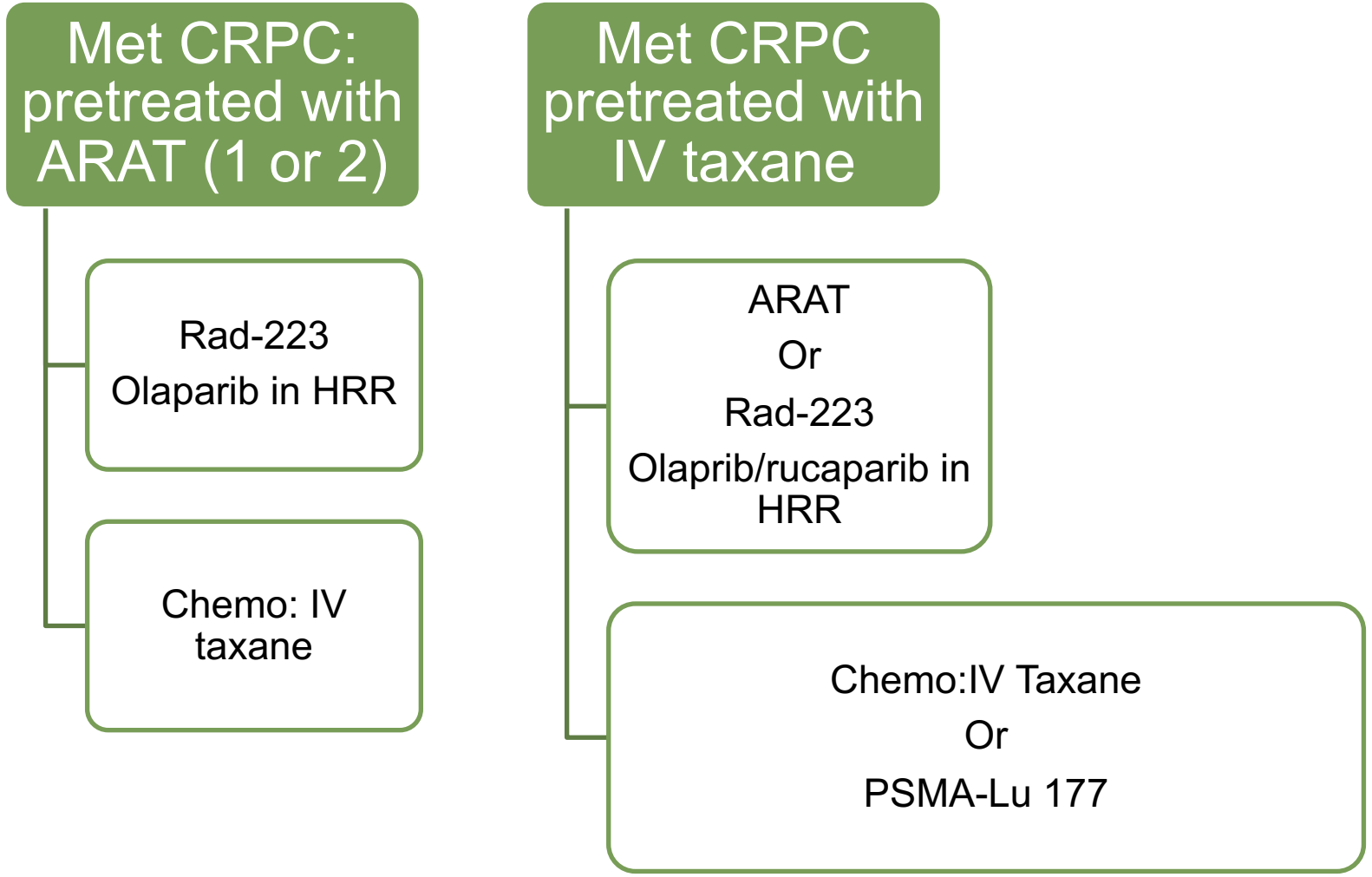
Summary of Approved Therapies with Survival Benefit in mCRPC

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 for HRR mutations, MSI high, TMB and CDK12



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”

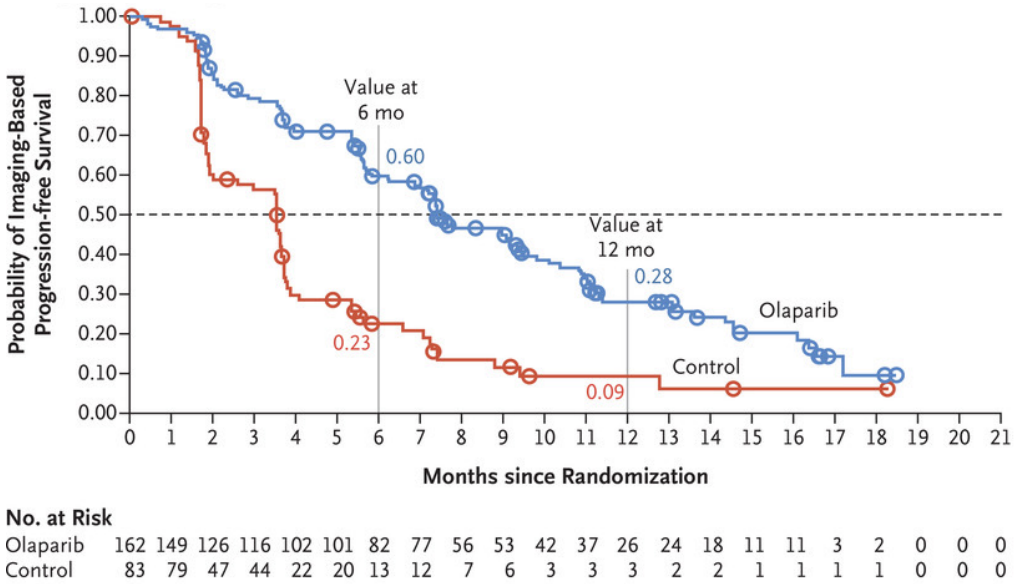
Mateo J et al. *Eur Urol*. 2017;71:417-425.

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

Imaging-Based PFS in Cohort A

Median rPFS, months

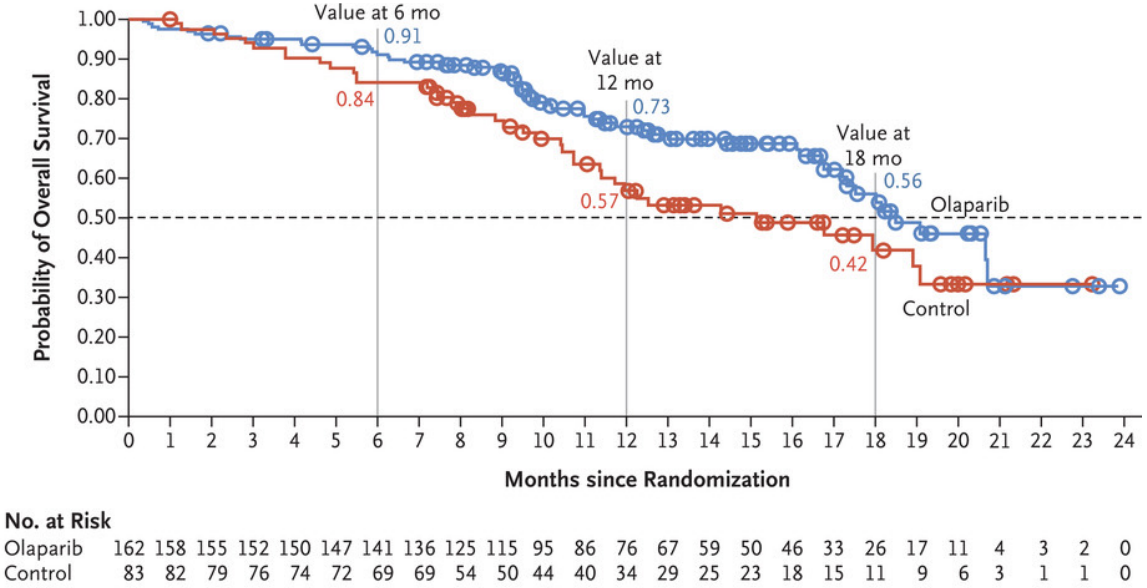
Olaparib 7.4
Control 3.6
HR, 0.34 (95%CI, 0.25-0.47); *P* < 0.0001



Interim OS in Cohort A

Median Interim OS, months

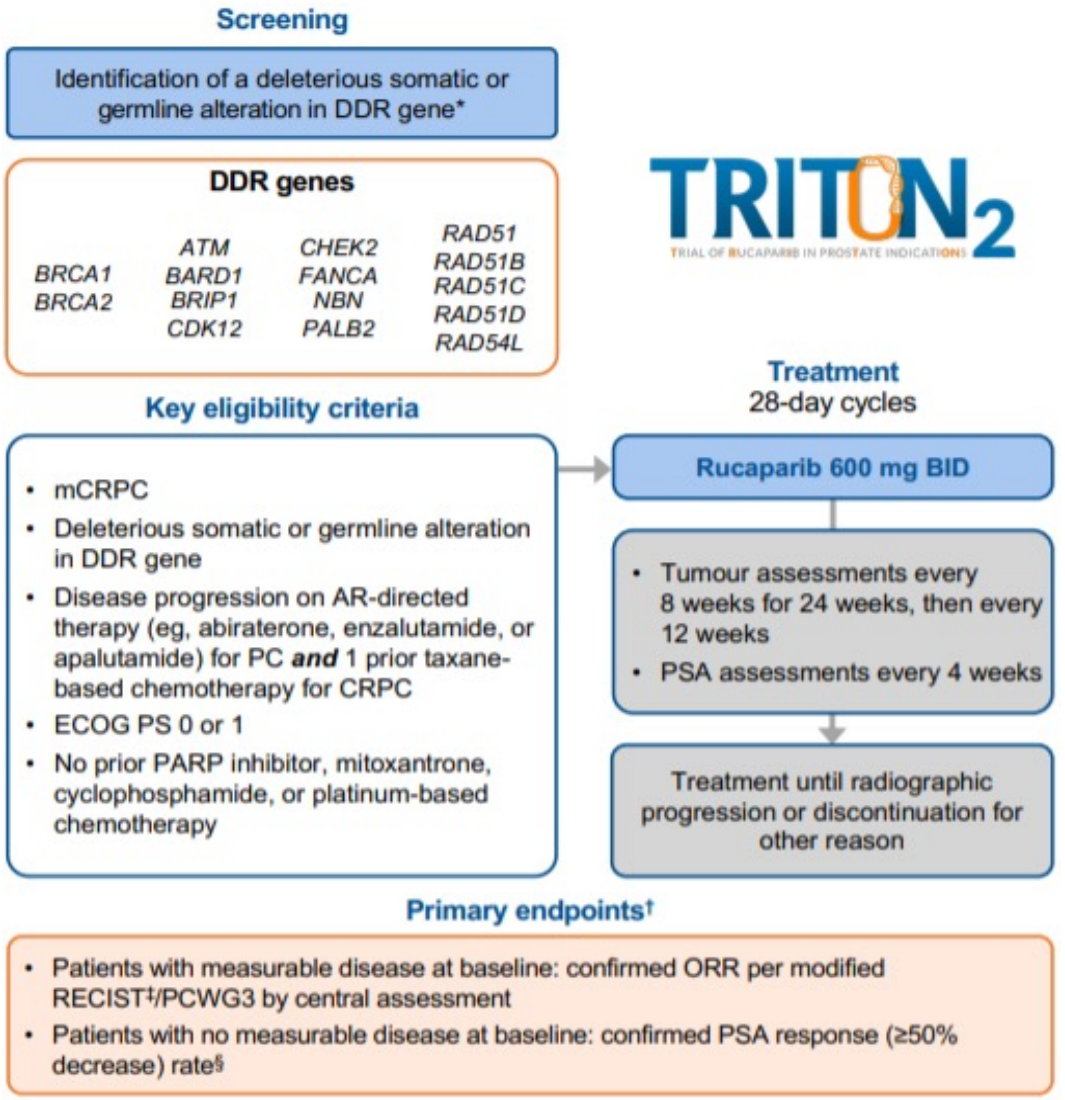
Olaparib 18.5
Control 15.1
HR, 0.64 (95%CI, 0.43-0.97); *P*=0.02



Figures from. de Bono et al.. *N Engl J Med.* 2020; 382:2091-2102

Phase II TRITON2: Rucaparib in mCRPC

- Phase 2 study rucaparib 600 mg BID
- mCRPC and a deleterious germline or somatic 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



Abida W, et al. *Ann Oncol*. 2019;30:mdz248.003. doi.org/10.1093/annonc/mdz248.003.

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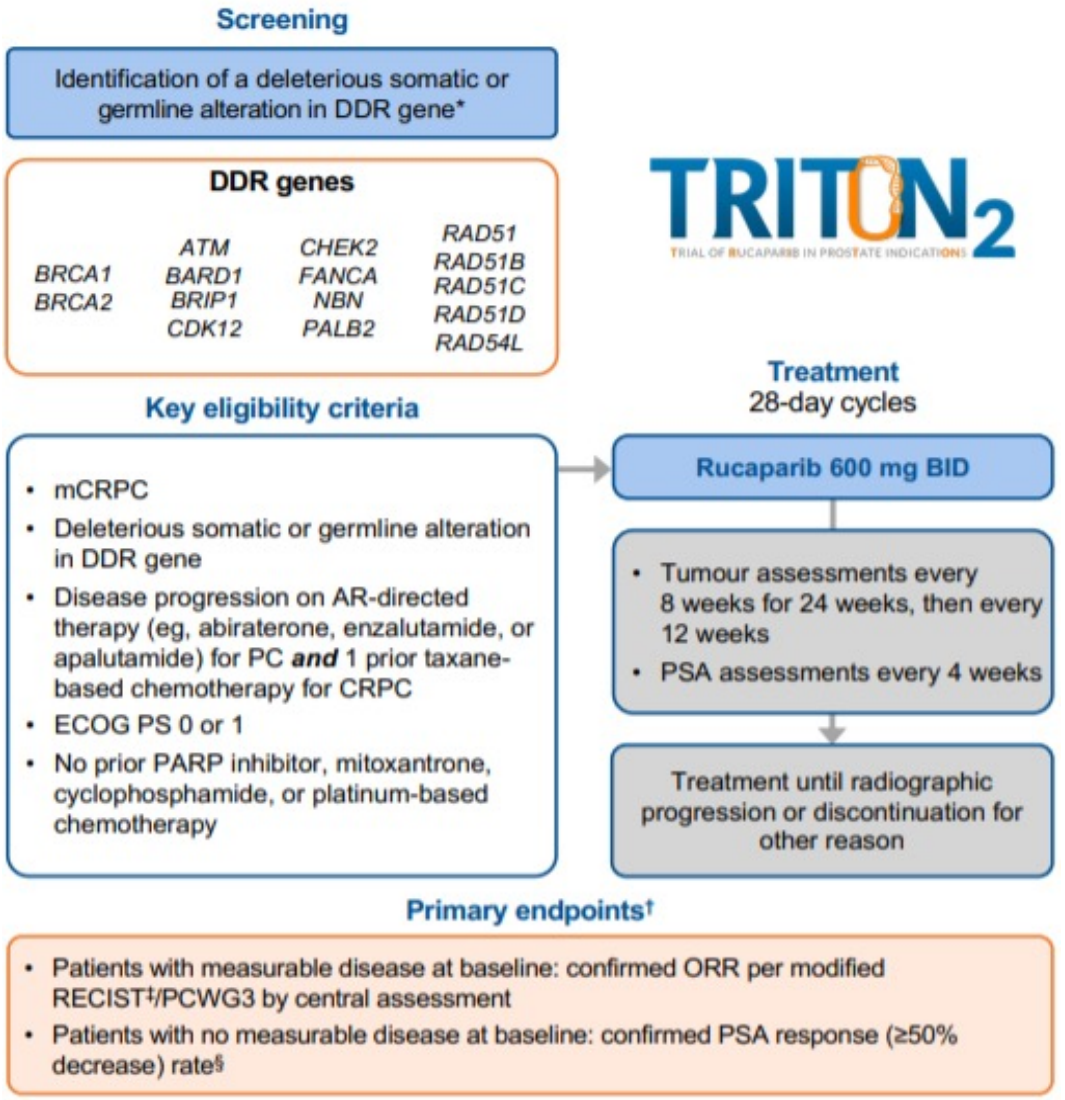
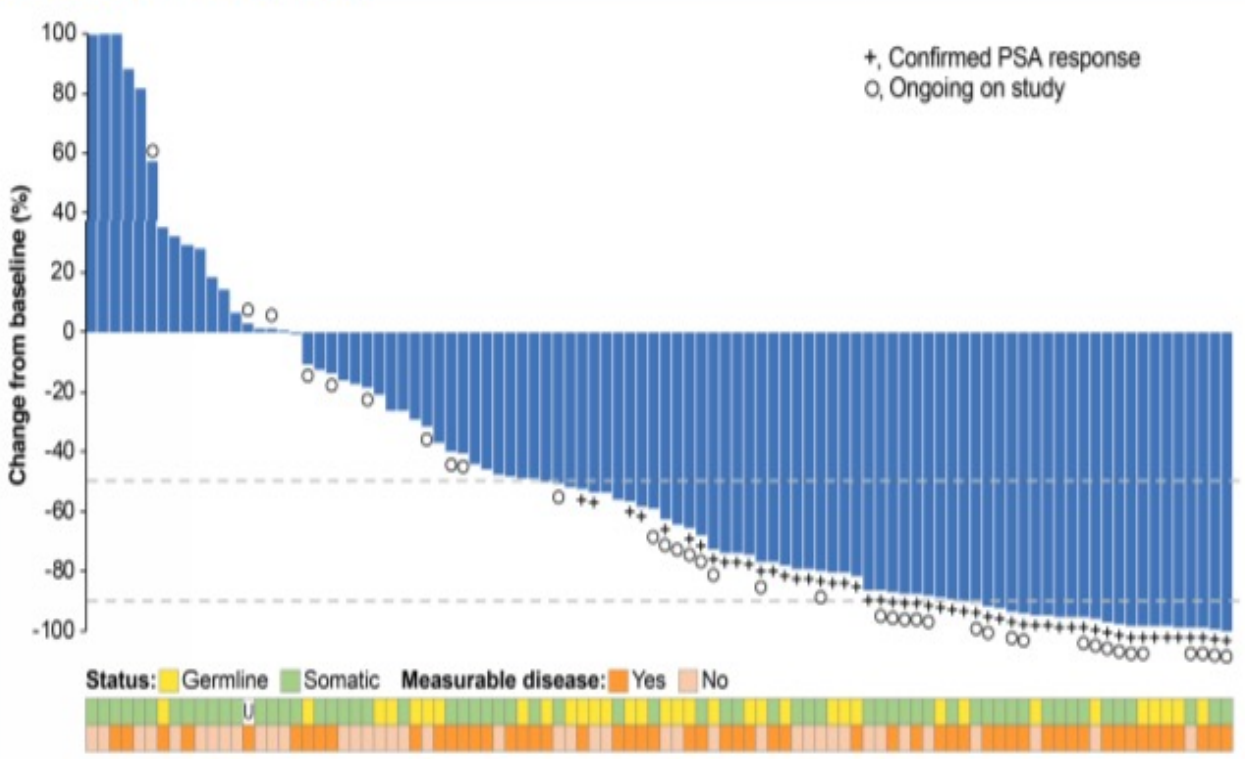


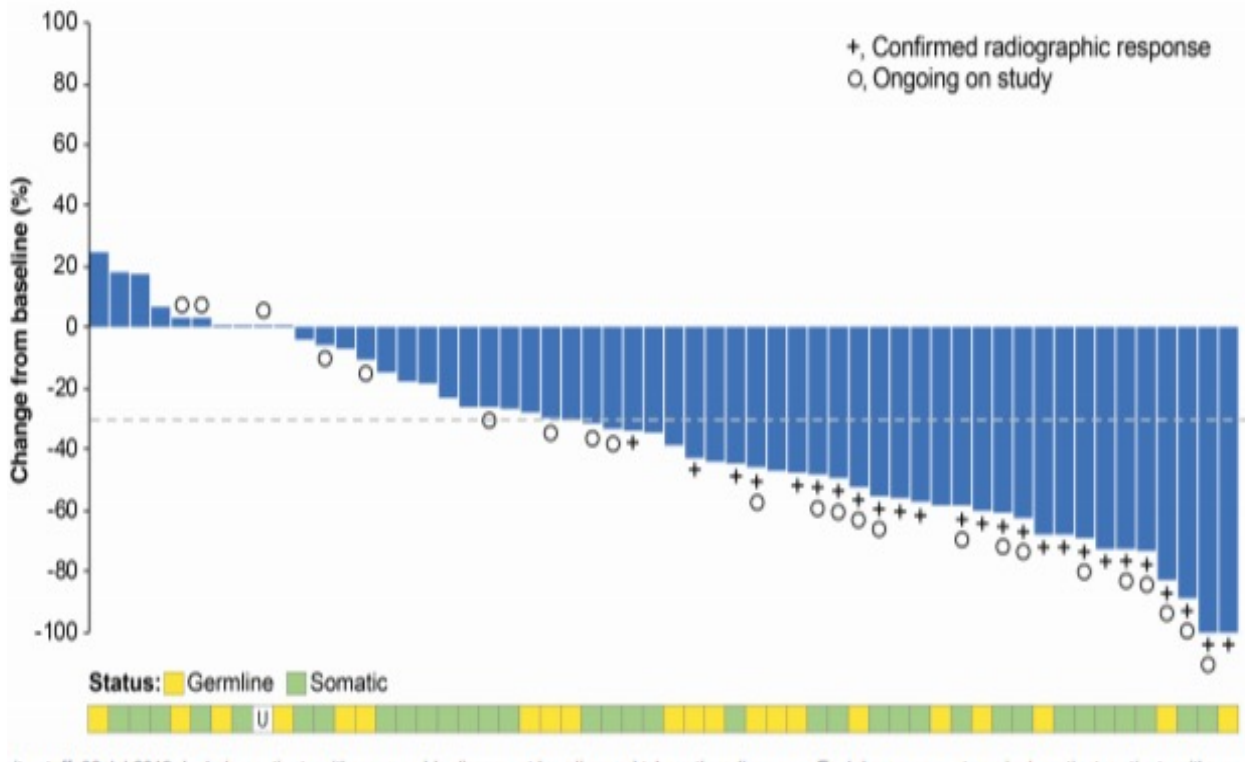
Abida W, et al. *Ann Oncol*. 2019;30:mdz248.003. doi.org/10.1093/annonc/mdz248.003.

Phase II TRITON2: Rucaparib in mCRPC

Best Change from Baseline PSA in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=96)



Best Change from Baseline in Sum of Target Lesion in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=56)



Figures from Abida W, et al. *Ann Oncol*. 2019;30:mdz248.003.

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

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RESOURCES SUBSCRIBE

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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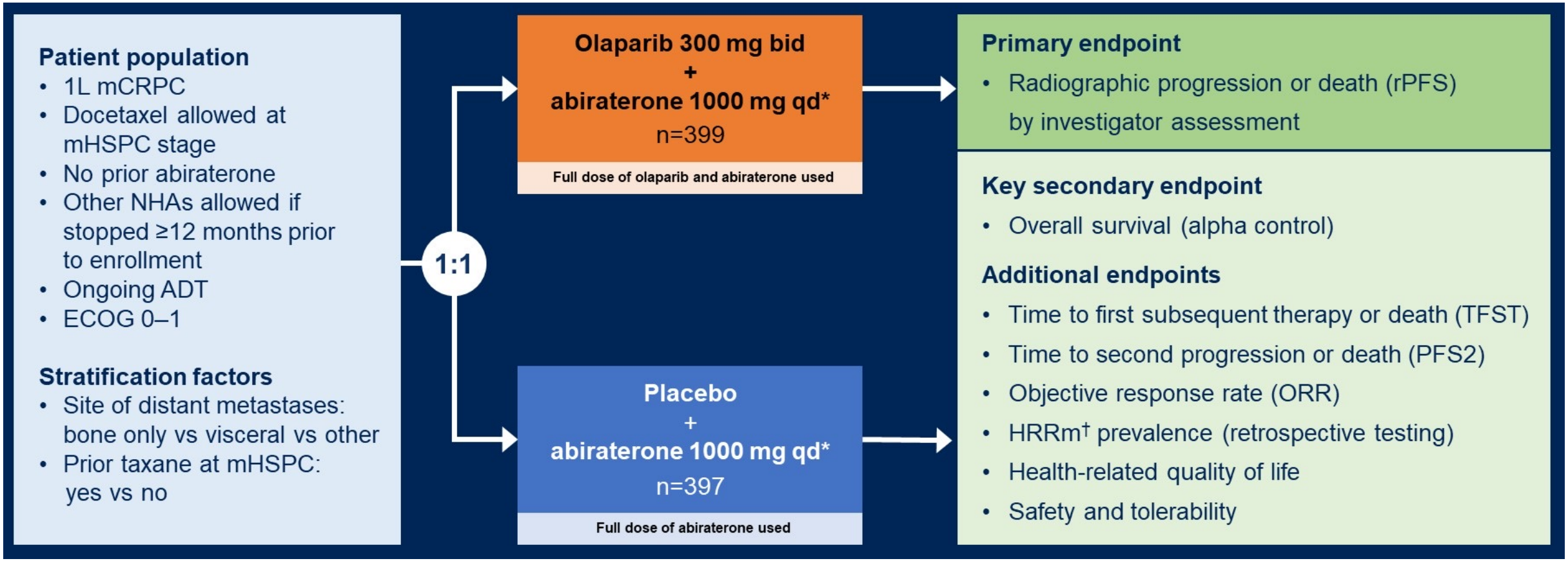
FDA Approves Olaparib for mCRPC Subset

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

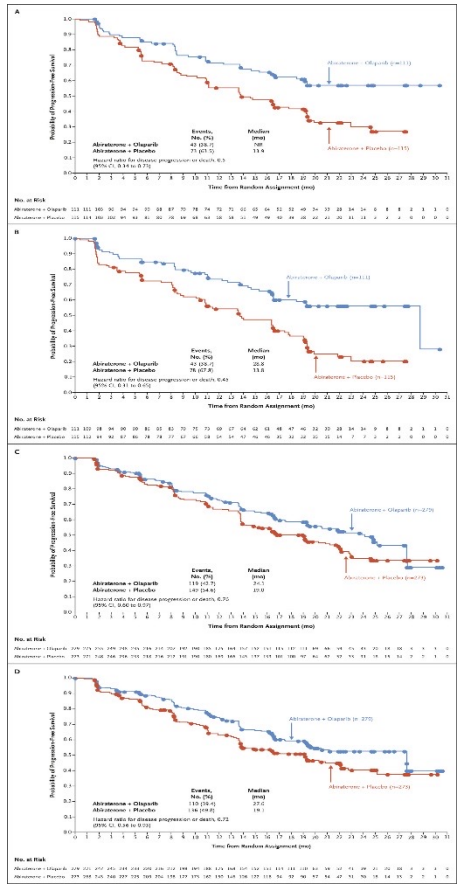
The FDA has approved olaparib for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide (Xtandi)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

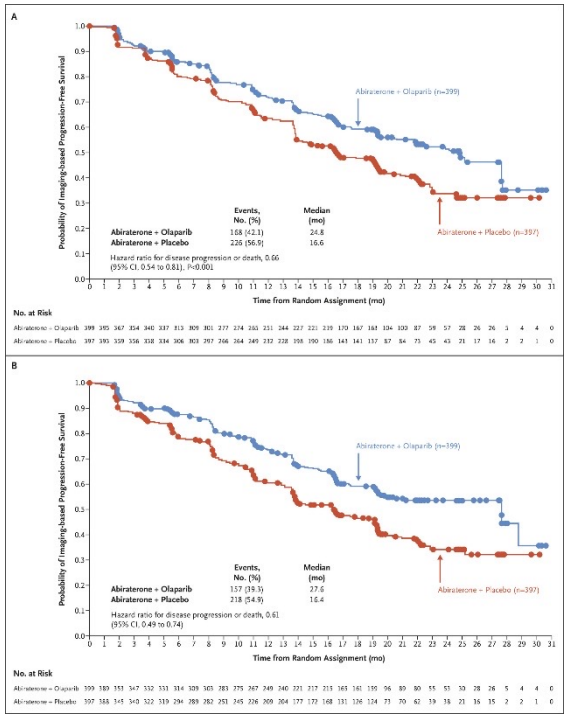
PROPEL STUDY
Clarke NW, et al NEJM Evidence 2022



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.





The Controversy of PARP inhibtiors in mCRPC Should this therapy be considered in unselected patients? Not with current evidence!

1)Propel trial showed PFS benefit but no OS benefit in all mCRPC patients

2) TALAPRO study showed PFS benefit but no OS benefit in all mCRPC patients

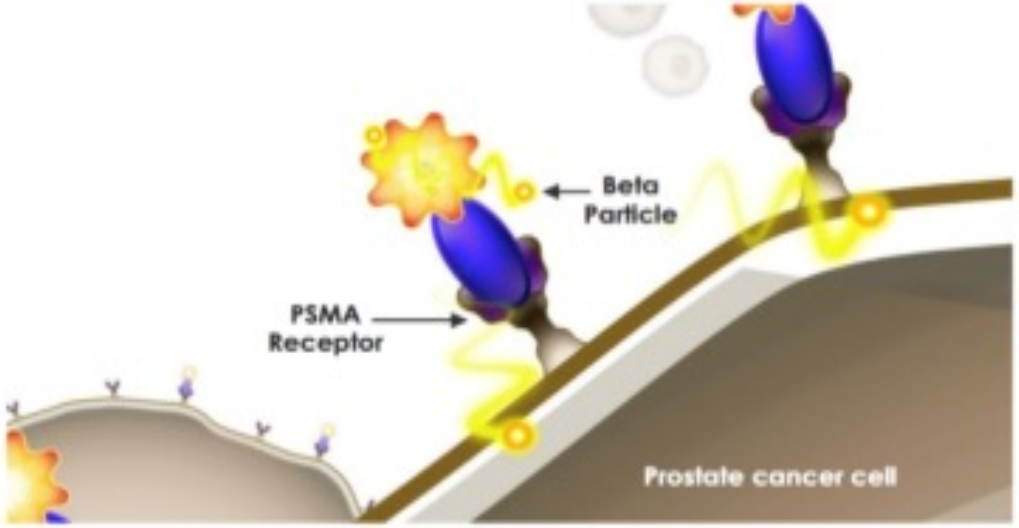
Magnitude trial: Niraparib + abiraterone showed benefit only in BRCA1/2 selected patients. Median PFS improvement by 6 months

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}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}lutetium atom releases an energetic beta particle that results in lethal radiation killing the cancer cell.

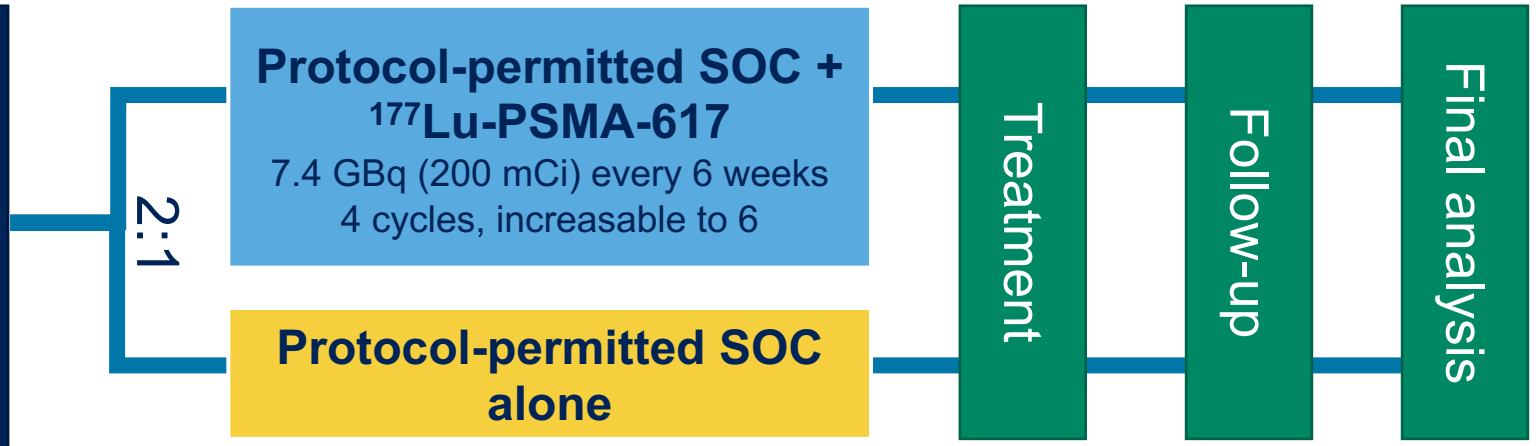
Benefits of Lutetium for Therapeutic Use

- 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

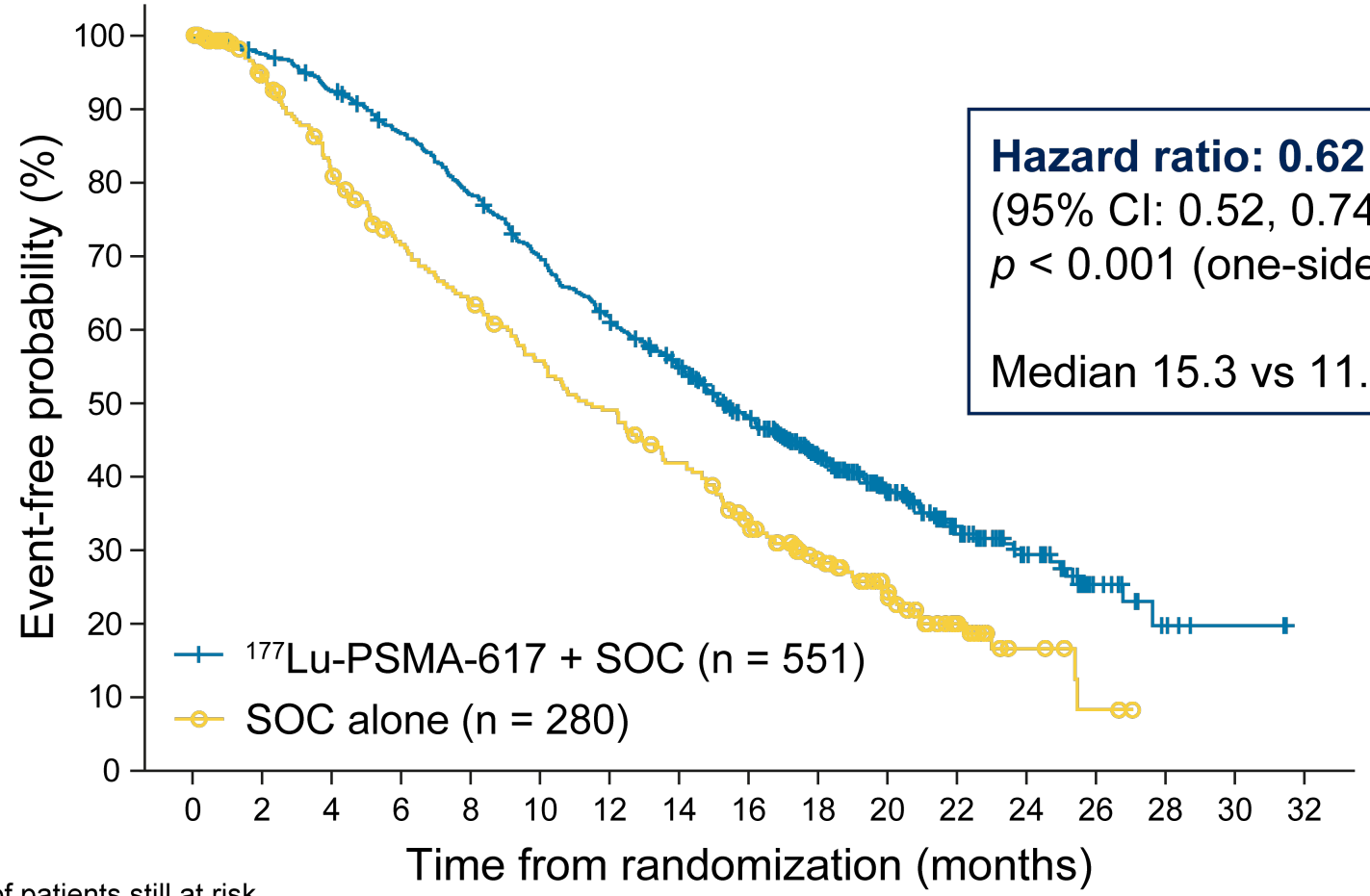


- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review

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

Primary analysis

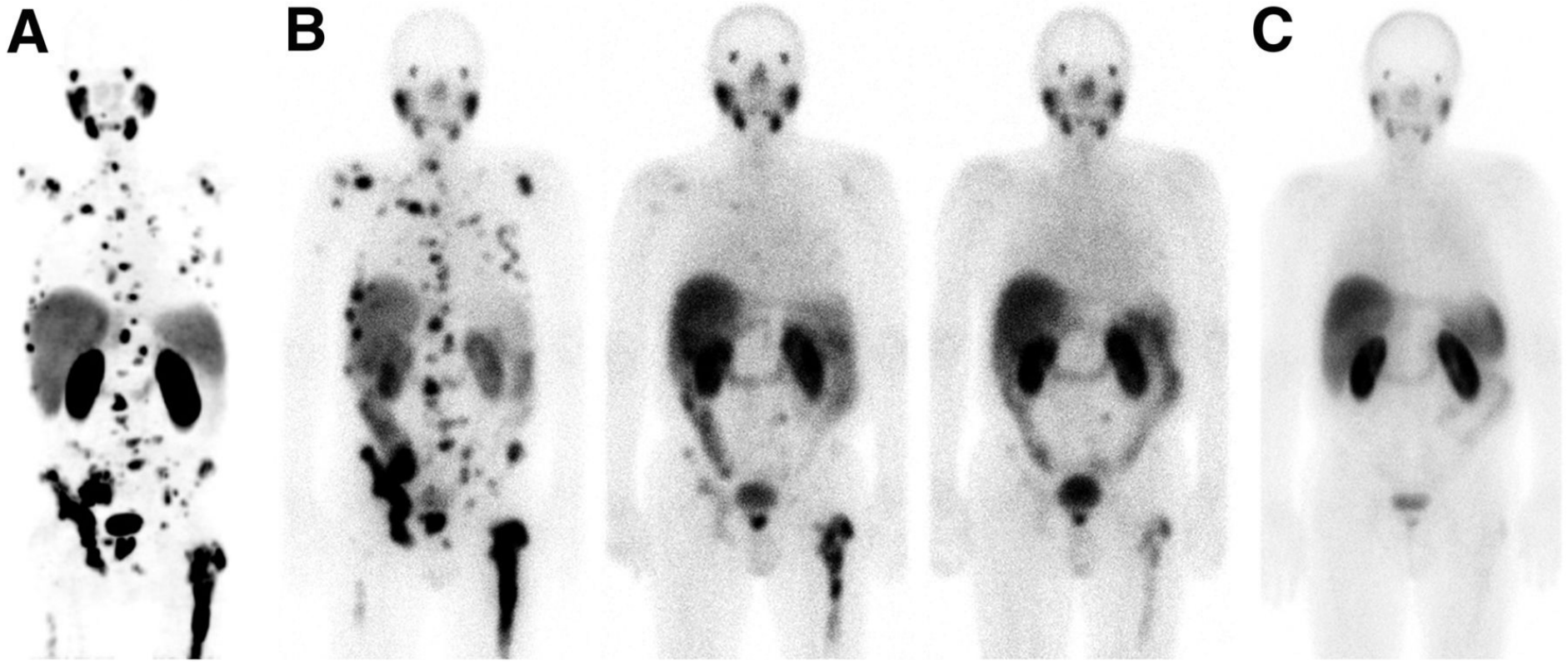
All randomized patients
(N = 831)



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

PSMA-Lu Response

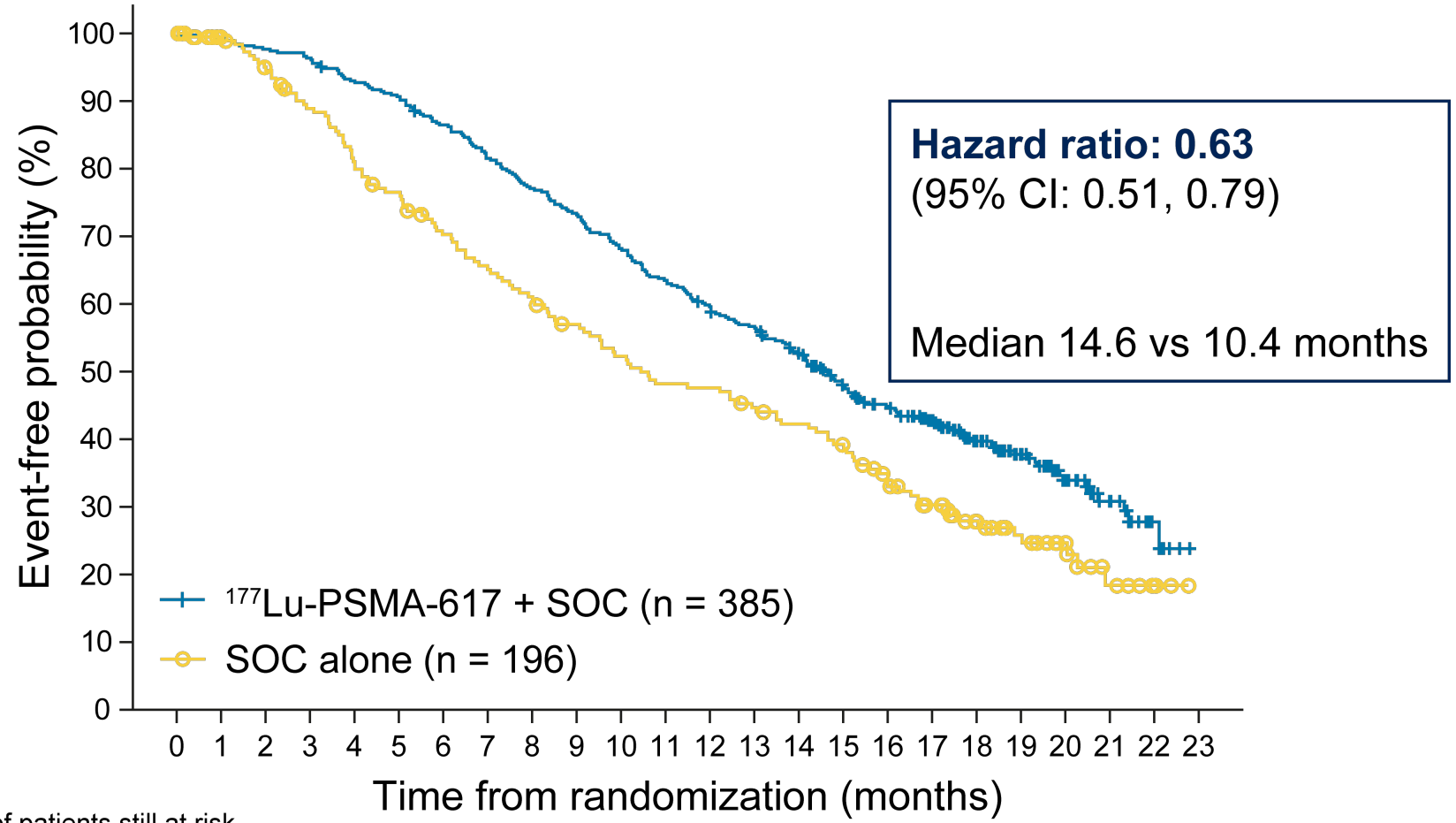


Kratochwil et al, 2016.

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

Additional analysis

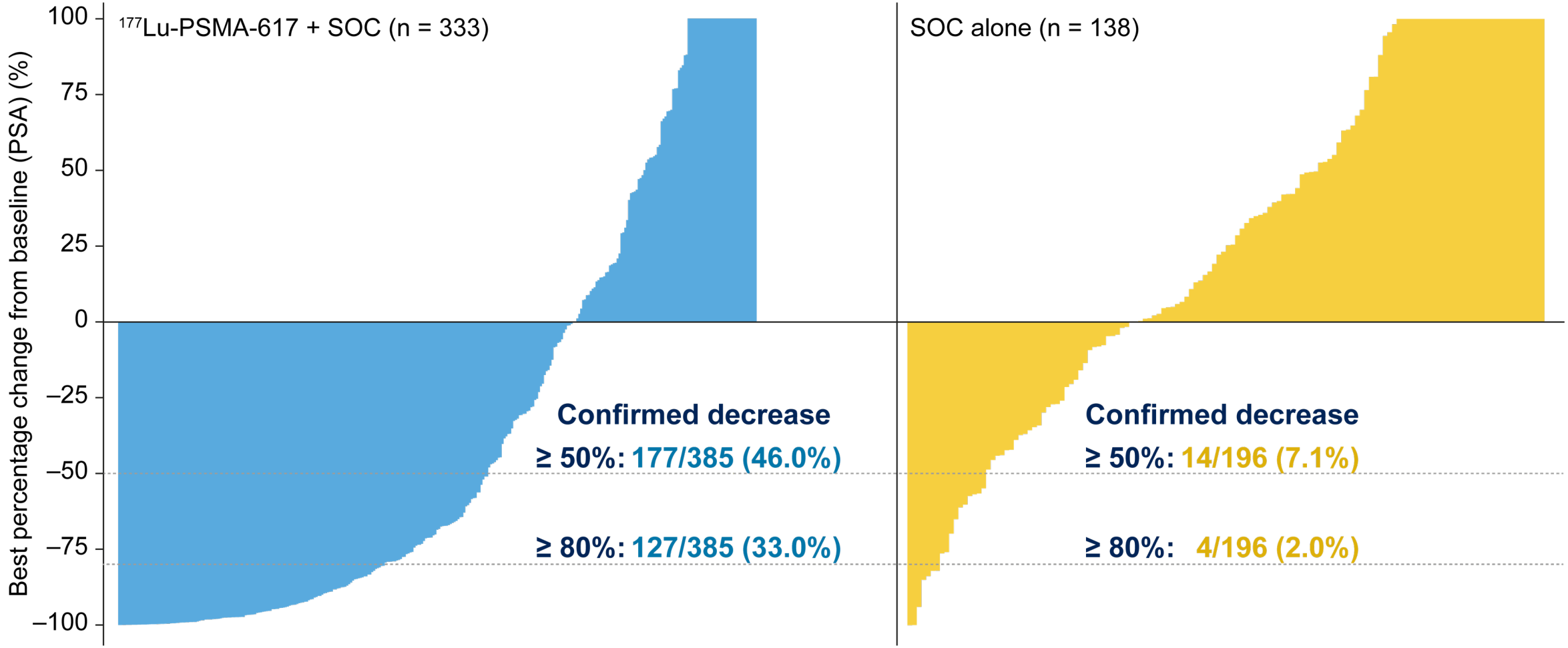
rPFS analysis set (n = 581)



Number of patients still at risk

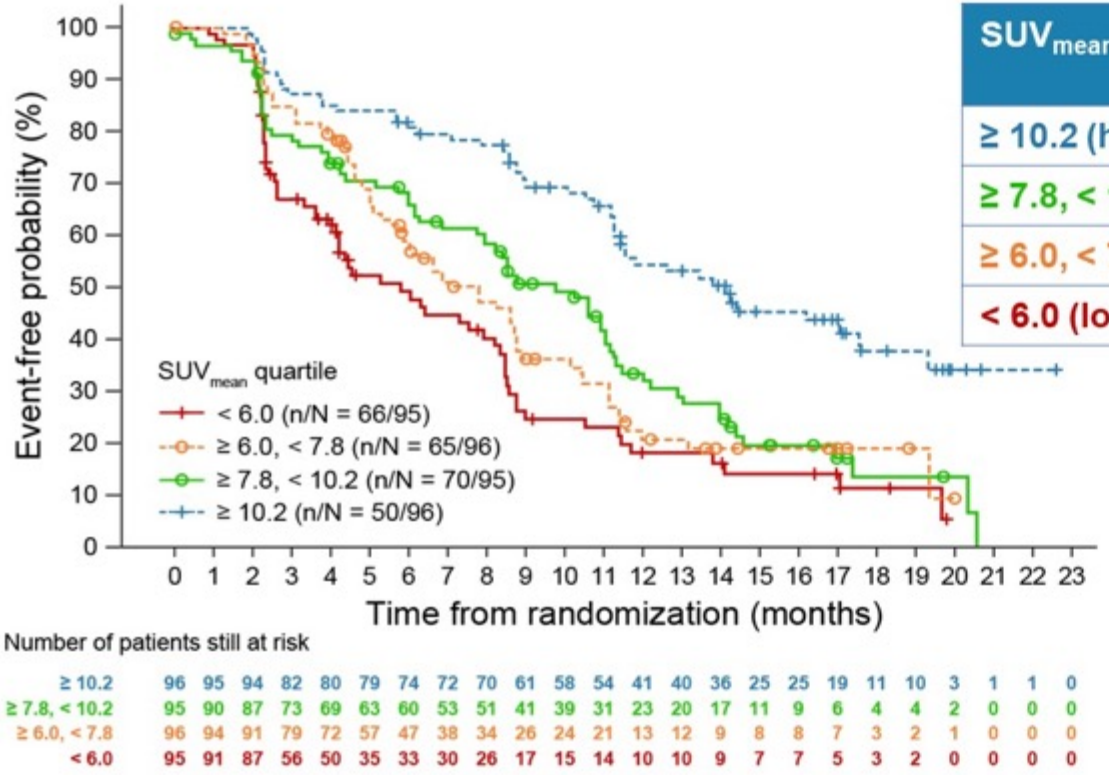
^{177}Lu-PSMA-617 + SOC	385	382	376	371	357	348	331	312	295	281	261	243	227	215	196	169	151	128	89	68	44	24	7	0
SOC alone	196	181	171	158	144	135	122	113	106	97	89	82	81	75	70	64	51	42	30	23	15	7	3	0

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**



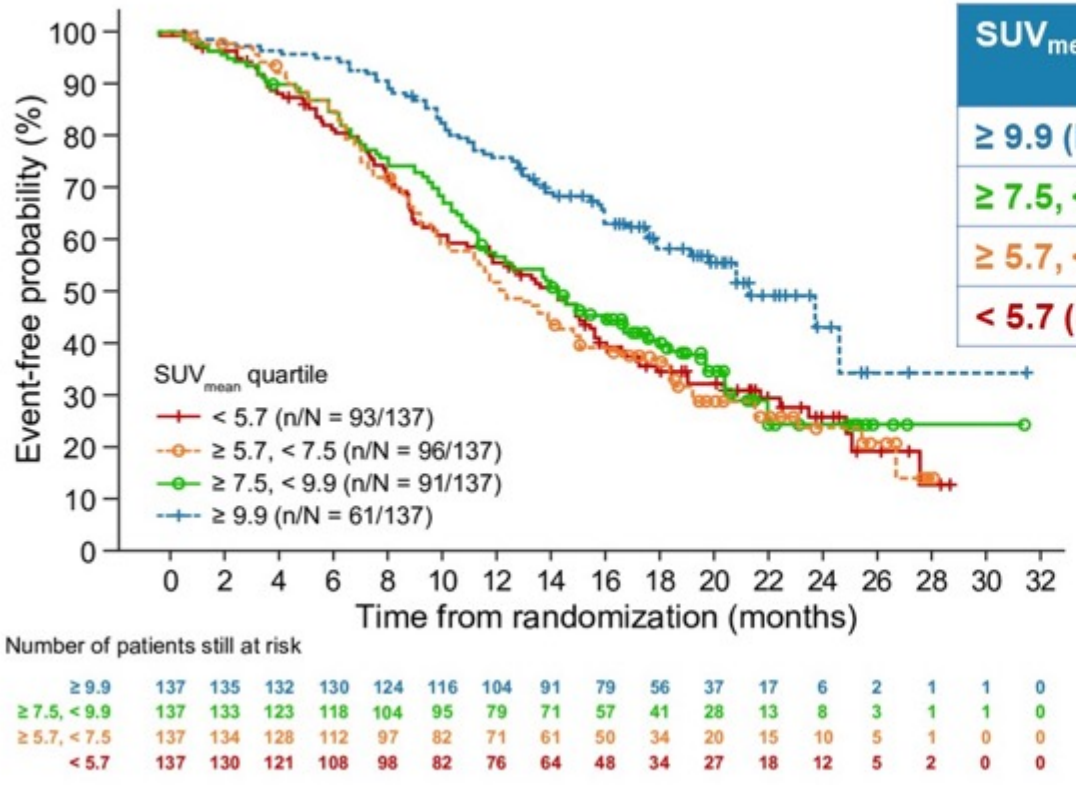
SUV_{mean} quartile	Median rPFS (months)
≥ 10.2 (highest)	14.1
≥ 7.8, < 10.2	9.8
≥ 6.0, < 7.8	7.8
< 6.0 (lowest)	5.8

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

Vae=rmstrong A et al. ASCO 2022

PSMA scan SUV mean correlated with OS

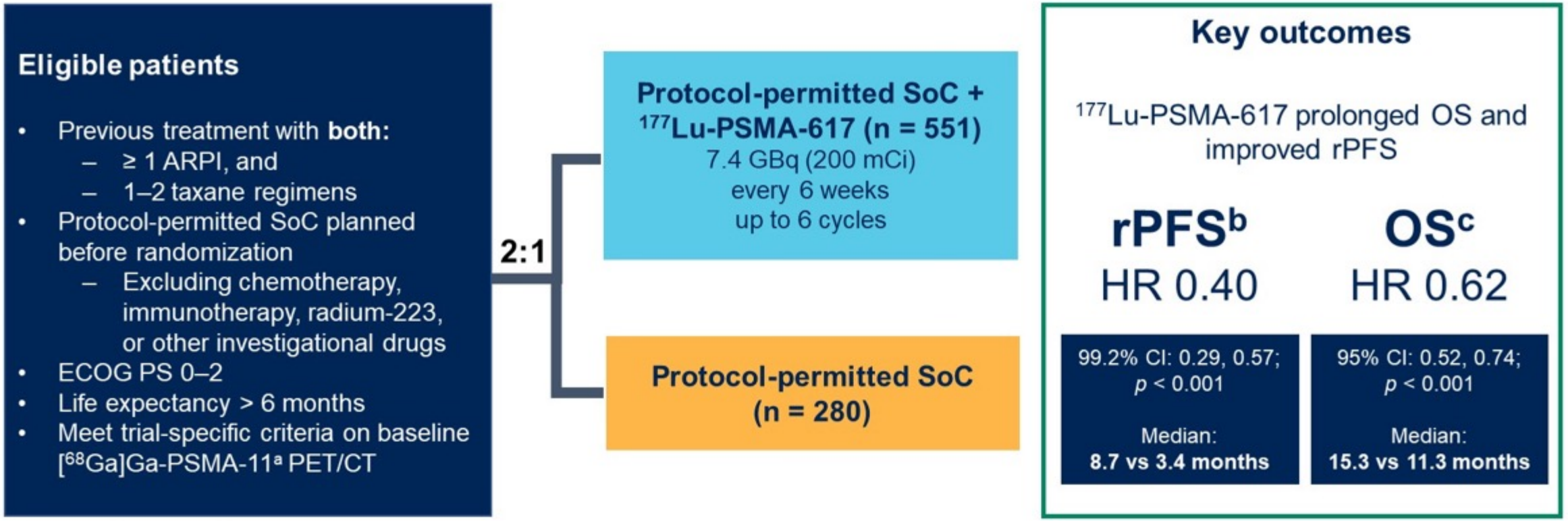
- **Higher whole-body SUV_{mean} was associated with improved OS**



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

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



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

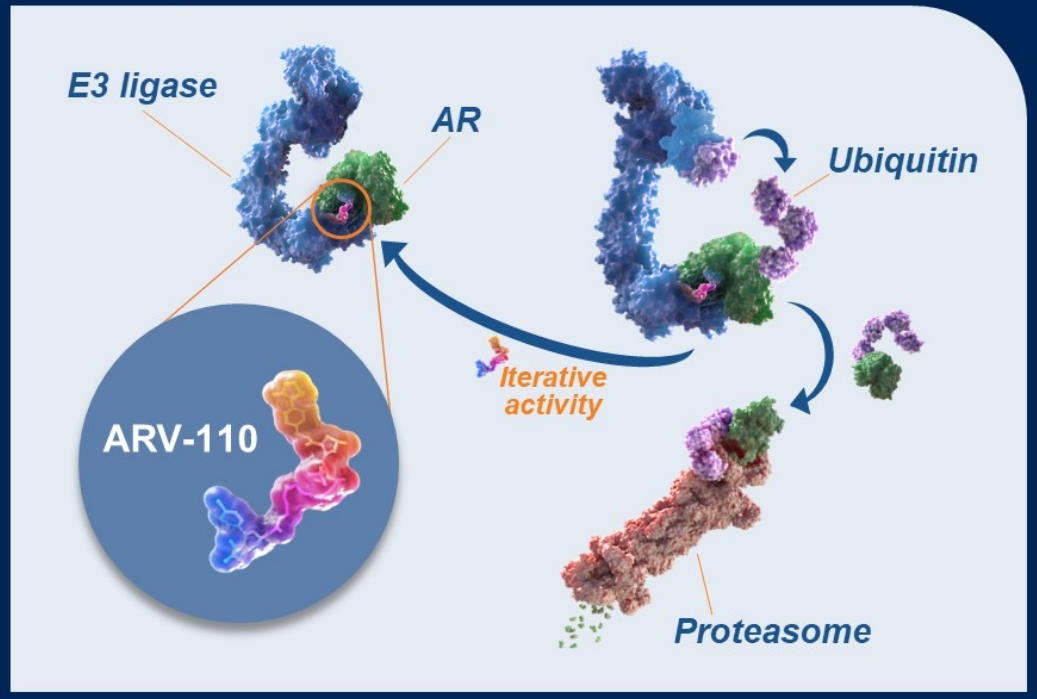
AR degraders

Oral chemo

Neuroendocrine Disease

Background

- Bavdegalutamide (ARV-110) is a novel, oral PROTAC protein degrader that targets wild-type AR and clinically relevant mutants



- In the phase 1 dose escalation study of ARV-110 in men with mCRPC who received ≥2 prior therapies (including abiraterone and/or enzalutamide)[1]:
  - An exposure-activity relationship was seen in heavily pretreated patients
  - Enhanced activity was observed in a biomarker-defined patient subset
    - PSA_{50} rate of 40% in patients with AR T878X/H875Y-positive tumors (n=5)
  - 420 mg QD was selected as the RP2D based on safety, PK, and efficacy*

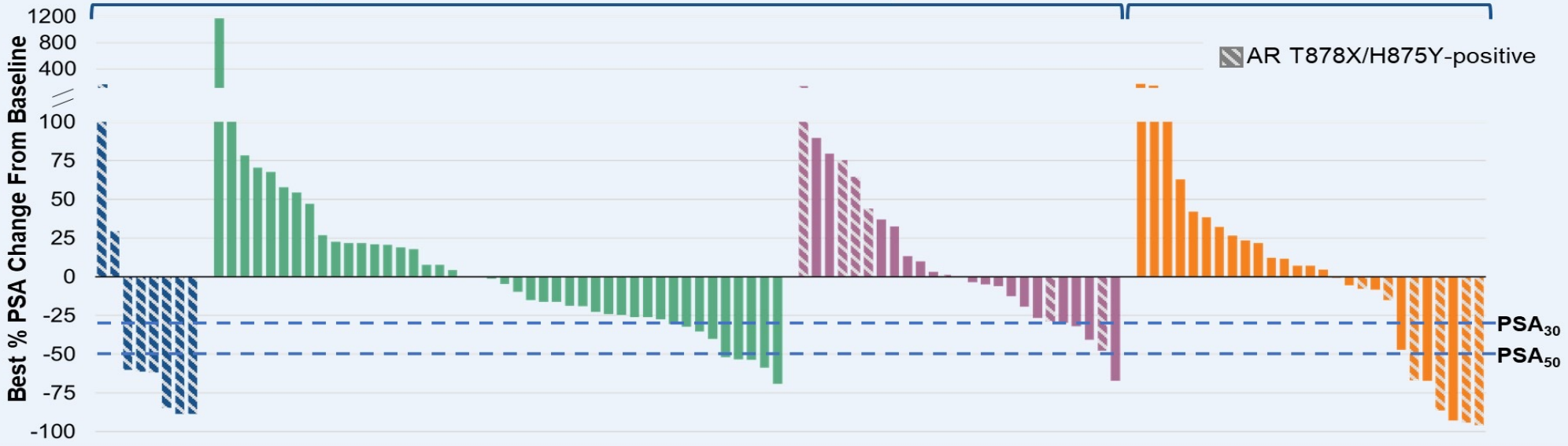
1. Chirnomas D, 28th Prostate Cancer Foundation Annual Scientific Retreat. 2021
*Doses ranged from 35–700 mg QD or 210–420 mg BID
AR=androgen receptor; BID=twice daily; DLT=dose-limiting toxicity; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetics; PROTAC=PROteolysis TArgeting Chimera; PSA=prostate-specific antigen; PSA_{50}=best PSA declines ≥50%; QD=once daily; RP2D=recommended phase 2 dose; T878X=T878A or T878S

Gao X, et al. ASCO GU Symposium 2023

Non-AR Molecular Profiles Were Similar in the Less Pretreated Subgroup and the More Pretreated, Biomarker-Defined Subgroups

	More Pretreated (Biomarker-Defined) (n=77)*
TP53	57%
BRCA2	8%
PI3K pathway	36%
RB1	9%

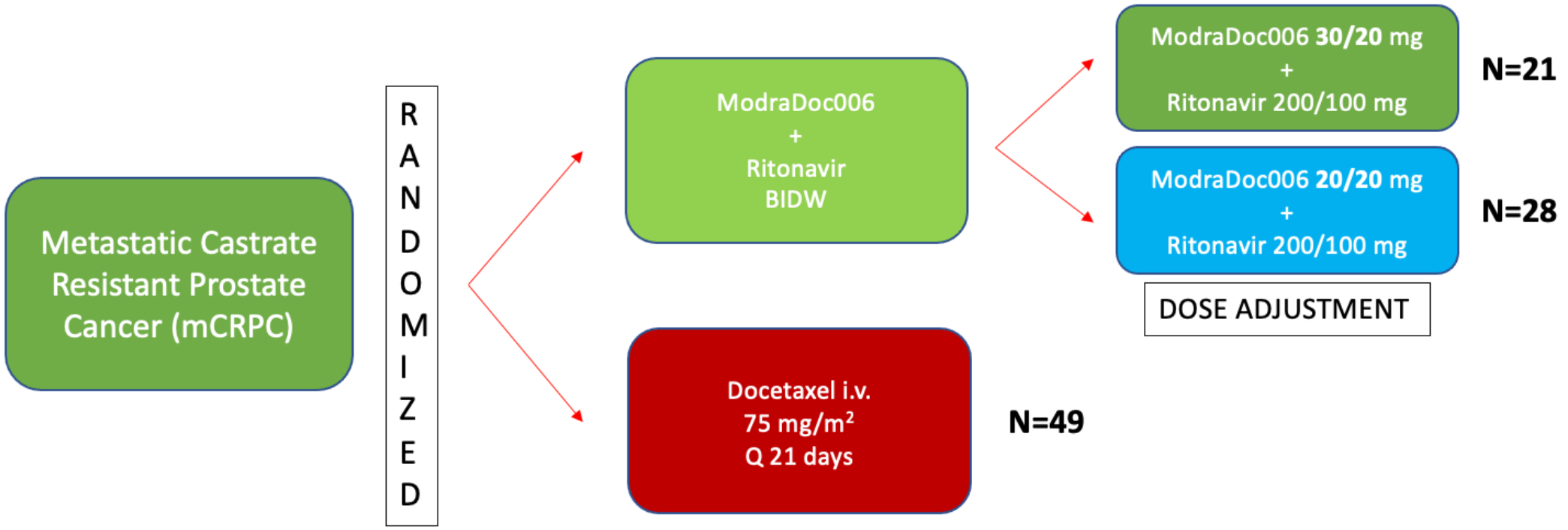
	Less Pretreated† (n=27)*
TP53	48%
BRCA2	15%
PI3K pathway	30%
RB1	11%



*Includes biomarker-evaluable patients with ≥4 weeks of PSA follow-up; non-AR molecular profile analyses are preliminary and exploratory
†All forms of AR
AR=androgen receptor; PSA=prostate-specific antigen; PSA_{30}=best PSA declines ≥30%; PSA_{50}=best PSA declines ≥50%; T878X=T878A or T878S

Gao X, et al. ASCO GU Symposium 2023

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

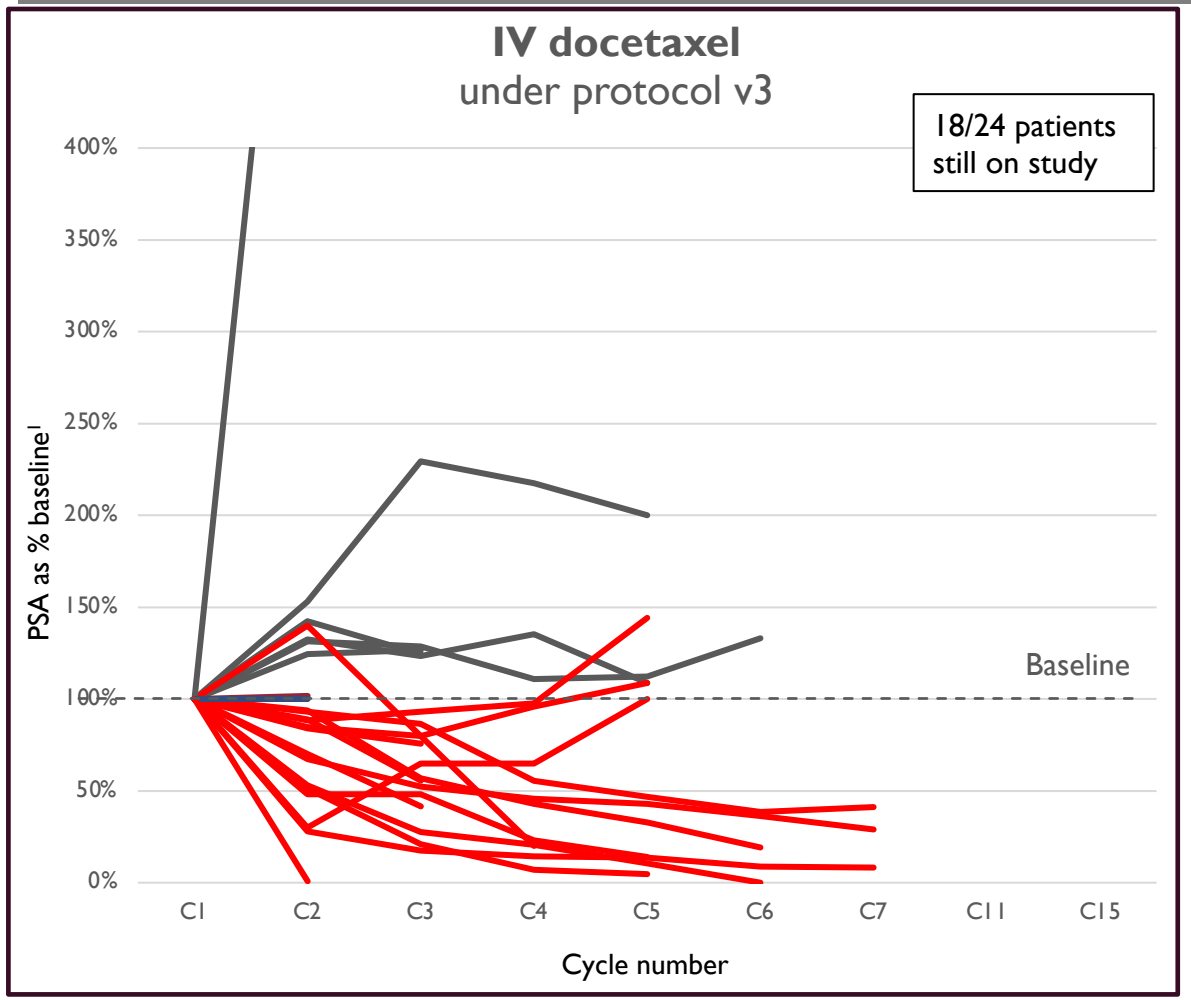


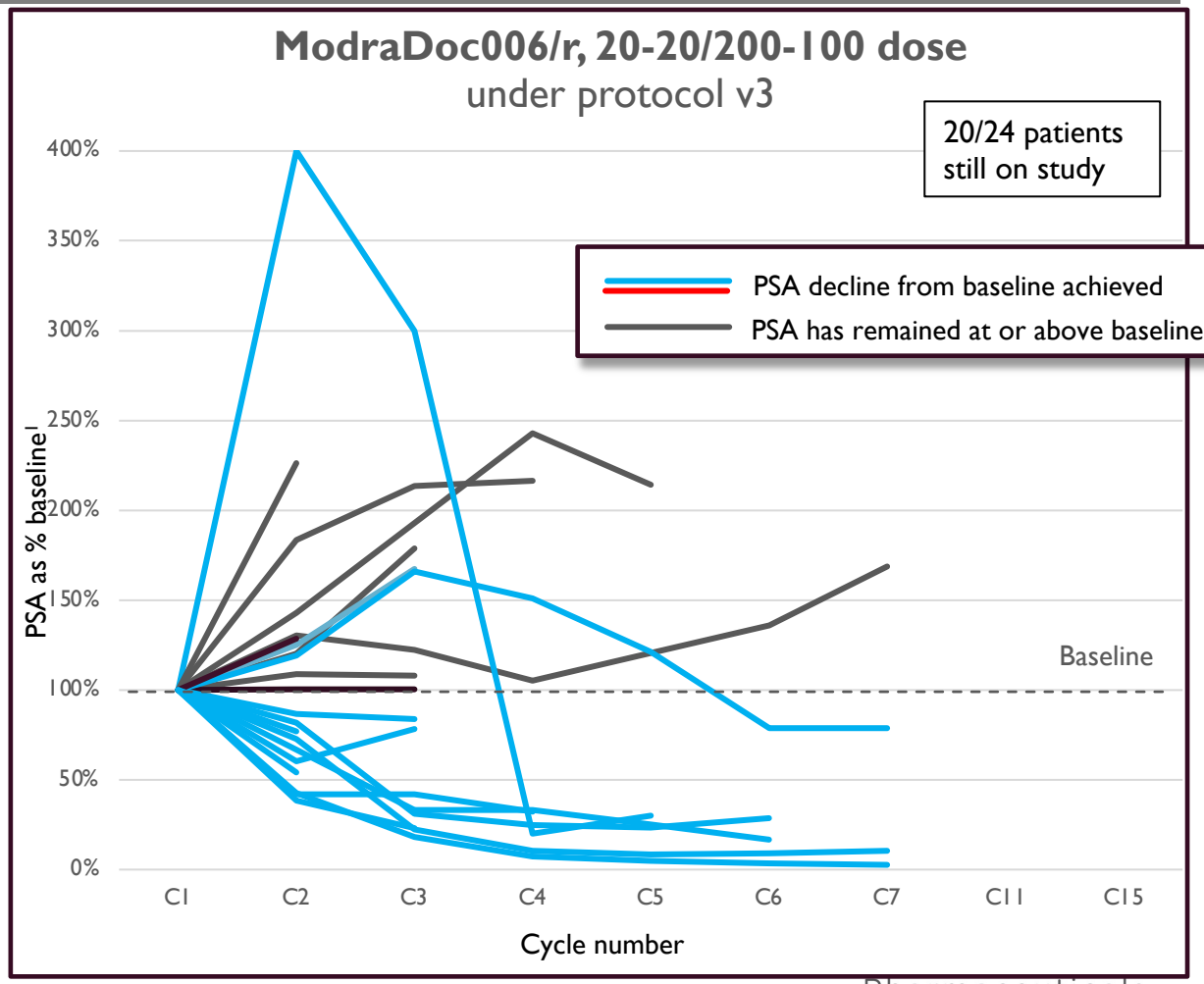
- Primary endpoint: rPFS
- Secondary: PSA RR, PFS@6m, TTP, DOR, PSA PFS,TT1stSkEv, ORR
- PI: Ulka Vaishampayan, University of Michigan

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





Pharmaceuticals

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

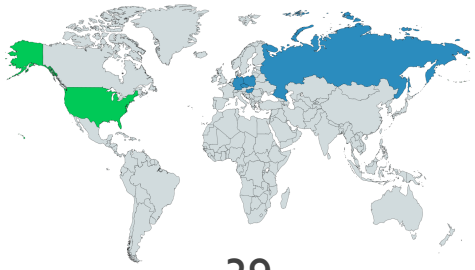
CONCLUSION

Safety

ModraDoc006/r typically exhibits mild GI-toxicities

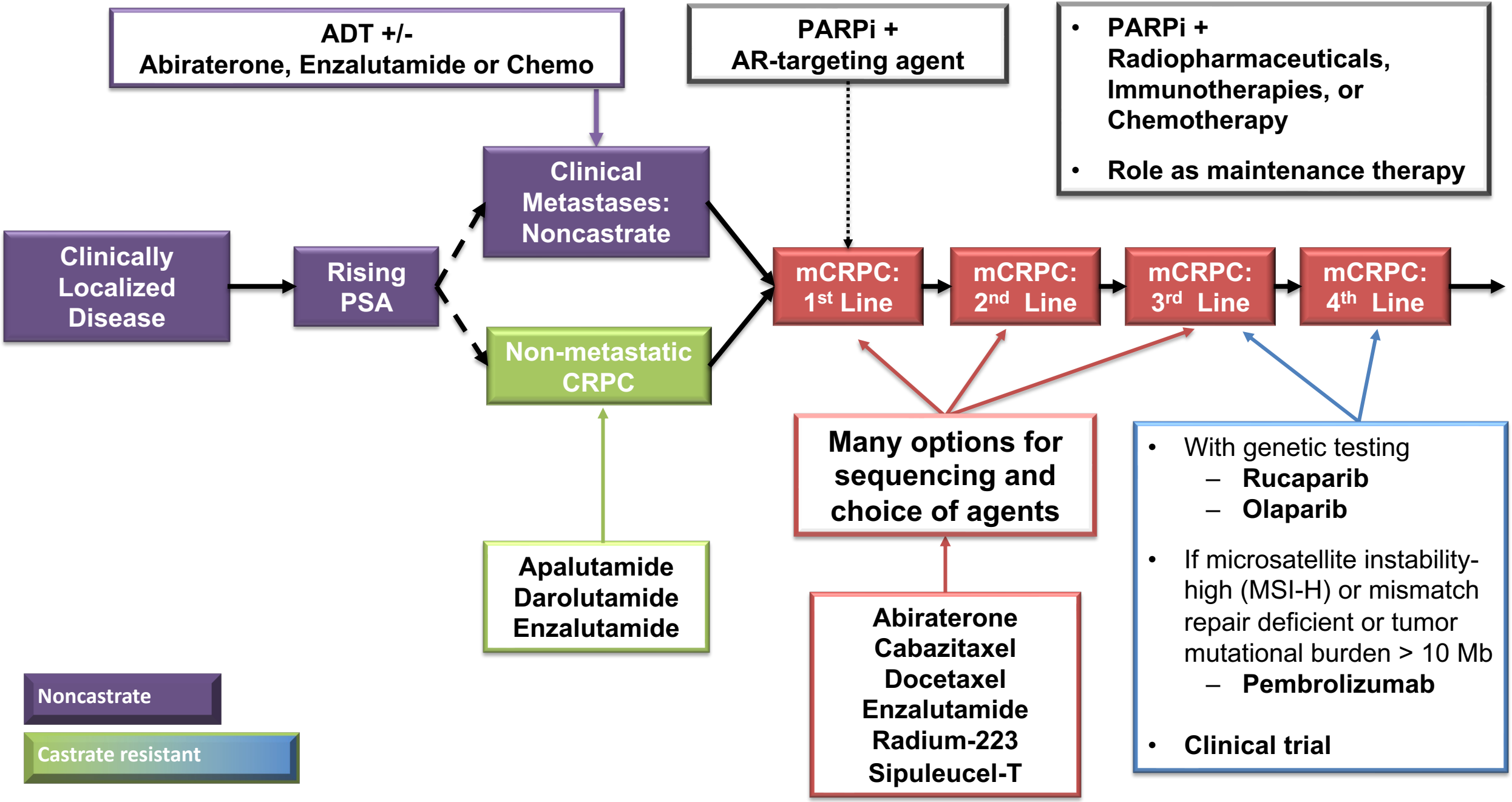
- No hematological toxicity at the 20-20/200-100 dose
- Elimination of infusion reactions
- Improved safety profile as compared to IV docetaxel with reduced cytopenias, infections and neuropathy.

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

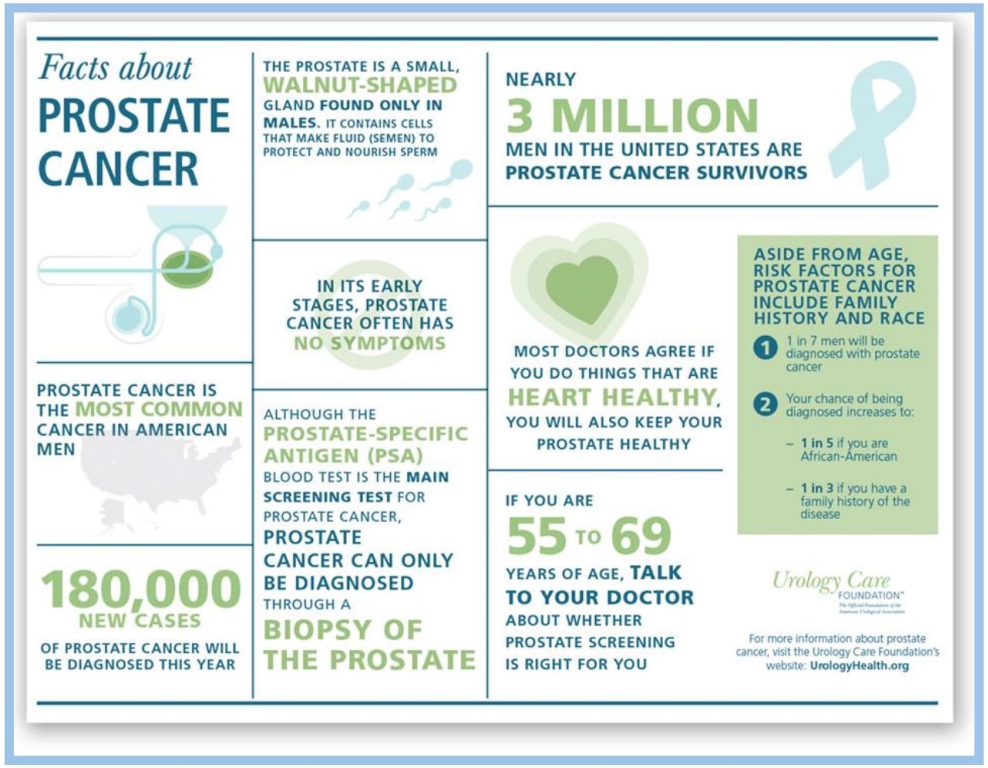
- Lenvatinib and pembrolizumab combination has established preclinical synergy: In syngeneic CT26 CRC and Hepa1-6 HCC murine tumor models, the combination of lenvatinib and an anti-PD-1 antibody produced greater reduction in tumor volume and a higher response rate than either agent alone, including complete 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.



Prostate Cancer Clinical States Model as developed by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) Guidelines. (Modified from Scher H,et al, *J Clin Oncol*. 2016;34(12):1402-18).

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



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...