Sequencing drugs in mCRPC

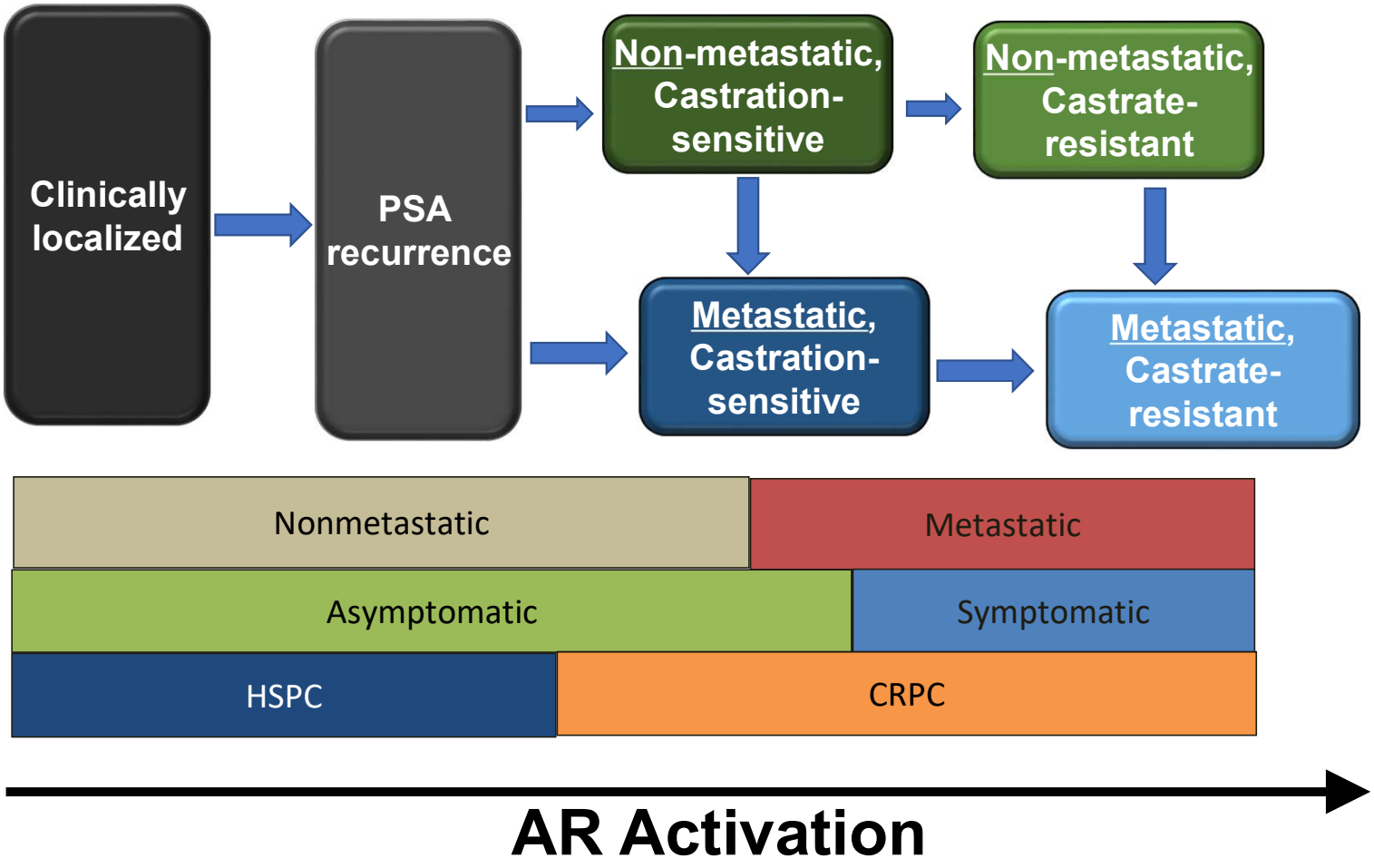
Sandy Srinivas.MD

Stanford University

Disclosures

- Advisory panel to Janssen & Bayer
- Clinical trials support with Bayer, Janssen

Clinical States of Prostate Cancer



Overview of Current Main Treatment Options for CRPC

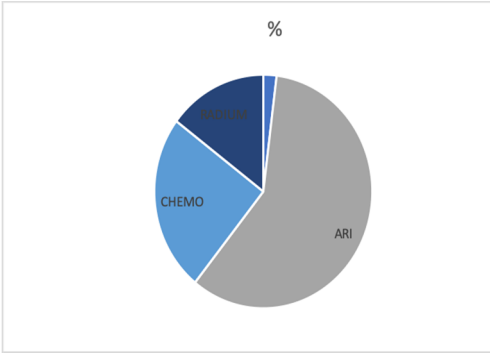
Nonmetastatic	Metastatic, asymptomatic/min sx	Metastatic chemotherapy naive	Metastatic, post docetaxel
Enzalutamide	Abiraterone	Docetaxel	Abiraterone
Apalutamide	Enzalutamide	Radium 223	Enzalutamide
Daralutamide	Sipuleucel-T	Abiraterone	Cabazitaxel
		Enzalutamide	Radium 223
		Strontium 89	Sipuleucel-T
		Samarium 153	Mitoxantrone
		Mitoxantrone	

Extends survival time (level 1 evidence)

Pain palliation only (level 1 evidence)

No level 1 evidence for outcome benefit

CLASSES OF DRUGS



Sequencing Drugs in CRPC

No level 1 evidence about the right sequence

Cross Resistance between ARI

Cross Resistance between chemotherapeutics

Delay time between the agents

Symptomatic vs asymptomatic

Bone disease vs non bone disease

Cross Resistance

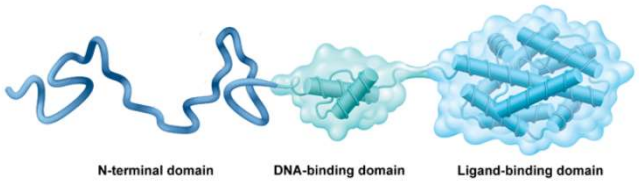
Abi/Enza. 60-78% 16-18

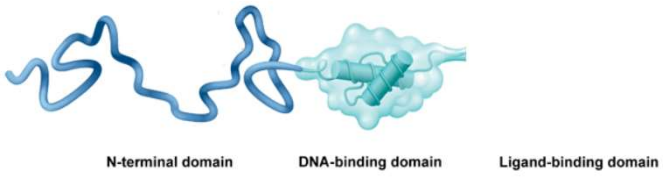
Ref	First Rx	Second	N	>50% PSA (%)	PFS mos
Loriot 2013 Ann Oncol	Enza	Abi	38	8	2.7
Noonan 2013 Ann Oncol	Enza	Abi	30	4	3.5
Schrader 2014 Eur Urol	Abi	Enza	35	28	-
Bianchini 2014 Eur J Cancer	Abi	Enza	39	12	2.8
Thomsen 2014 Sc J Can	Abi	Enza	24	17	
Petrelli 2015 Clin GU Can	Abi	Enza	536	22	3.1
Cheng 2015 Pros Can Proc	Abi	Enza	165	17	2.8
Azad 2015 Eur Urol	Abi	Enza	68	22	4.6

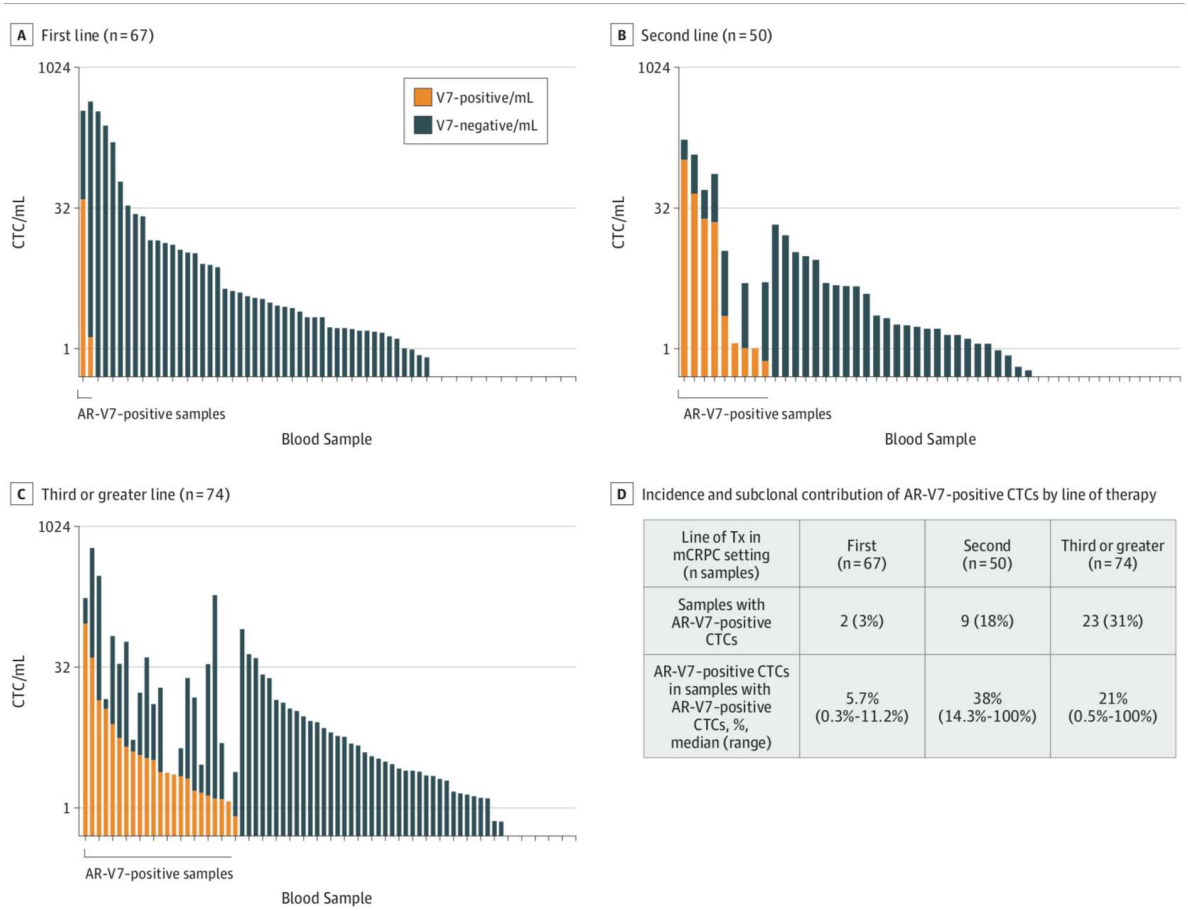
Sequence examples in CRPC

State	nmCRPC	HSPC	CRPC Bone only			
ARI start	Apalutamide/ Enzalutamide Daralutamide		Docetaxel	Radium-223	Abiraterone	Cabazitaxel
Chemo start		Docetaxel	Abiraterone	Radium-223	Cabazitaxel	Enzalutamide
ARI start		Abiraterone/ Enzalutamide Apalutamide	Docetaxel	Radium 223	Enzalutamide Abiraterone	Cabazitaxel
Sipuleucel T			Abi/enza	Radium 223/Doce	Enza/Abi	Cabazitaxel

ARV-7 Spice Variant



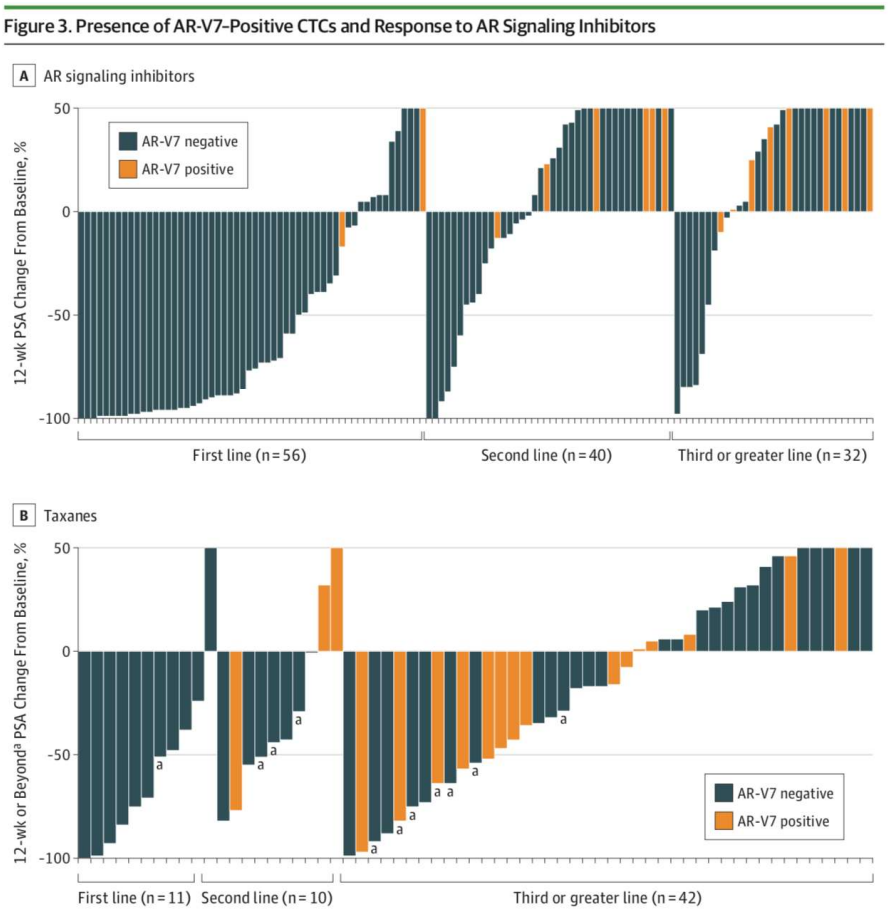


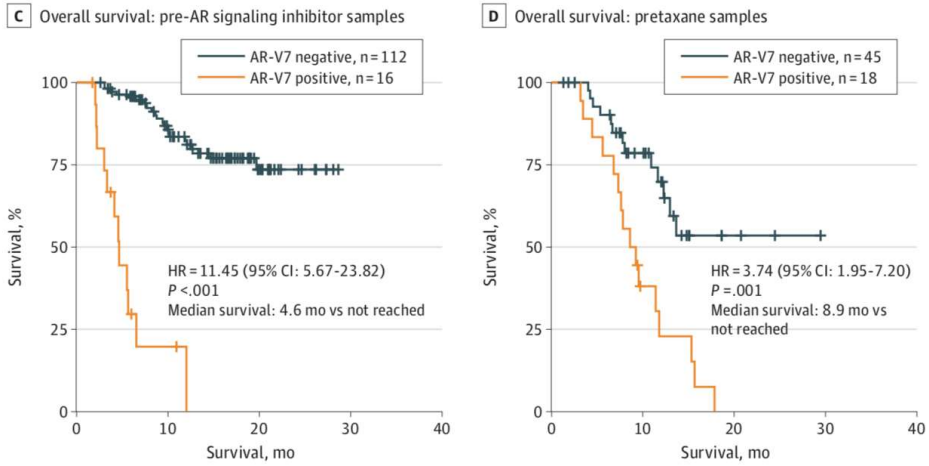


Line of Tx in mCRPC setting (n samples)	First (n = 67)	Second (n = 50)	Third or greater (n = 74)
Samples with AR-V7-positive CTCs	2 (3%)	9 (18%)	23 (31%)
AR-V7-positive CTCs in samples with AR-V7-positive CTCs, %, median (range)	5.7% (0.3%-11.2%)	38% (14.3%-100%)	21% (0.5%-100%)

Matias PM et al. J Biol Chem 2000

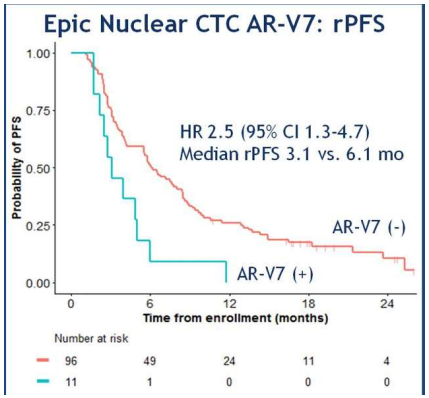
ARV-7 and PSA responses to ARI/Taxanes

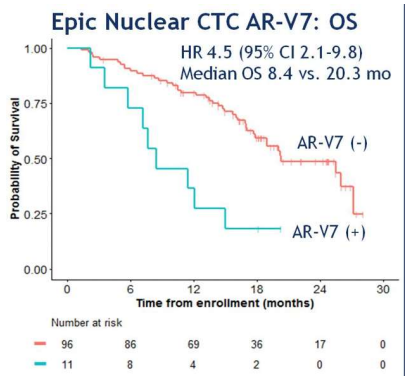


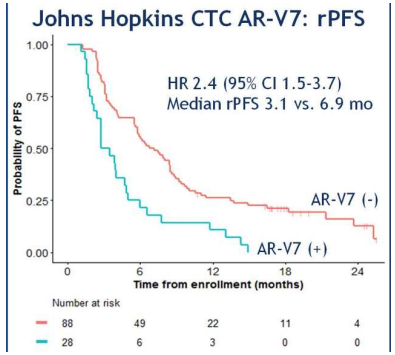


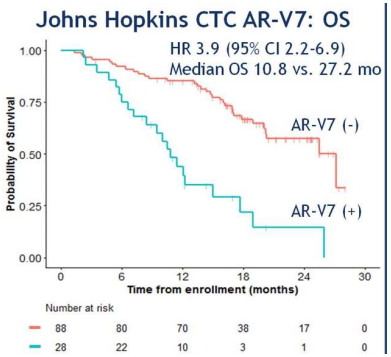
Prophecy : Prospective trial ARV7

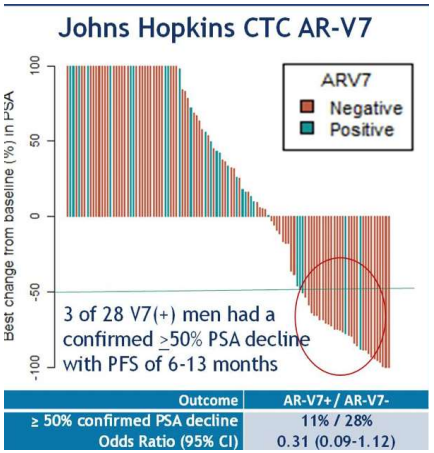
CTC Test	Pre-Specified Positive Test
JHU CTC AR-V7 Adnatest (RNA)	EpCAM selected, AR/PSA/PSMA+ CTC RNA with detectable AR-V7 mRNA at <36.14 RT-PCR cycles (2)
Epic CTC AR-V7 nuclear protein	Presence of CTCs (CK+ or -) expressing nuclear AR-V7 protein (1)

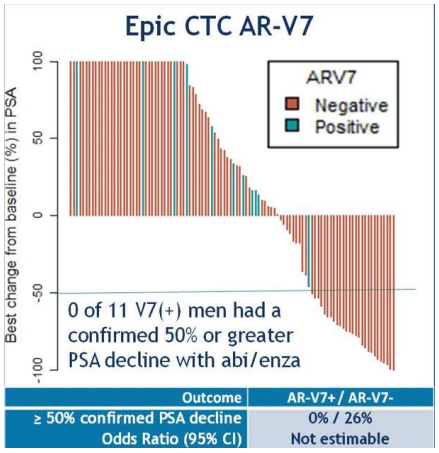












Armstrong, ASCO 2018

Germline DNA-Repair Gene Mutations in Men With Metastatic Prostate Cancer

- Analysis of 20 DNA-repair genes in men with mPC (N = 692)
  - 82 men (11.8%) had total of 84 germline mutations across 16 DNA-repair genes
  - DNA-repair gene mutations less common in locally advanced prostate cancer (4.6%)
    - Unclear association with family history!

Most Frequently Mutated Genes in mPC,* %	Prevalence
BRCA2	5.35
CHEK2	1.87
ATM	1.59
BRCA1	0.87
GEN1	0.46
RAD51D	0.43
PALB2	0.43

BRCA1/2: higher gleasons, increase metastases and worse OS; CSS 8.6 yrs vs 15.7 years

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

Screening

Identification of a deleterious somatic or germline alteration in HRR gene*

HRR genes

BRCA1	*BARD1*	*FANCA*	*RAD51B*
BRCA2	*BRIP1*	*NBN*	*RAD51C*
ATM	*CDK12*	*PALB2*	*RAD51D*
	CHEK2	*RAD51*	*RAD54L*

TRITON2
TRIAL OF RUCAPARIB IN PROSTATE INDICATIONS

Key eligibility criteria

- mCRPC
- Deleterious somatic or germline alteration in HRR gene
- Disease progression on AR-directed therapy (eg, abiraterone, enzalutamide, or apalutamide) for PC ***and*** 1 prior taxane-based chemotherapy for CRPC
- ECOG PS 0 or 1
- No prior PARP inhibitor, mitoxantrone, cyclophosphamide, or platinum-based chemotherapy

Treatment
28-day cycles

Rucaparib 600 mg BID

- Tumour assessments every 8 weeks for 24 weeks, then every 12 weeks
- PSA assessments every 4 weeks

Treatment until radiographic progression or discontinuation for other reason

Primary endpoints†

- Patients with measurable disease at baseline: confirmed ORR per modified RECIST‡/PCWG3 by central assessment
- Patients with no measurable disease at baseline: confirmed PSA response (≥50% decrease) rate§

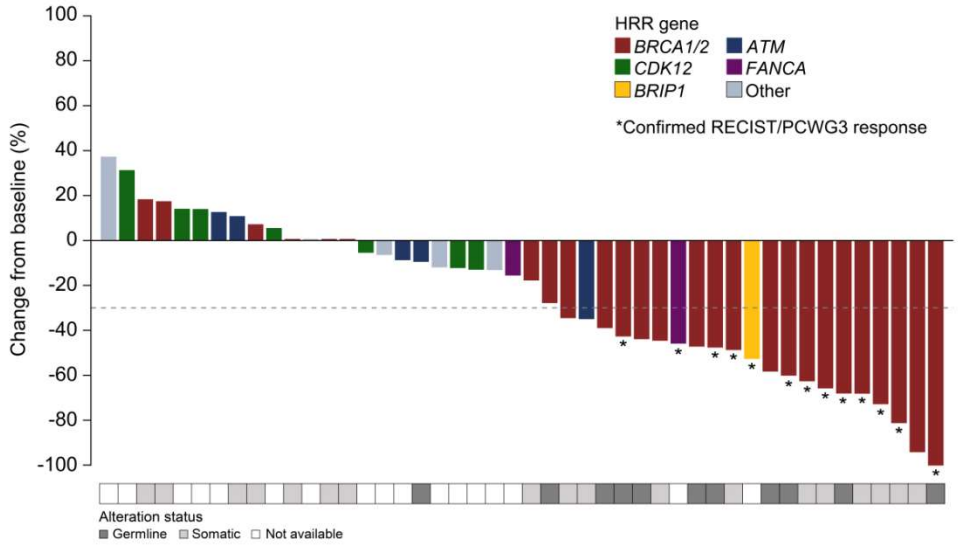
Chowdhury et al, ESMO 2018

Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

Characteristic	By HRR gene with alteration			
	BRCA1/2 (n=25)	*ATM* (n=5)	*CDK12* (n=8)	Other (n=8)
ORR, n (%) [95% CI][a]	11 (44.0%) [24.4–65.1]	0 [0.0–52.2]	0 [0.0–36.9]	2 (25.0%) [3.2–65.1]
Complete response, n (%)	0	0	0	0
Partial response, n (%)	11 (44.0%)	0	0	2 (25.0%)[b]
Stable disease, n (%)	9 (36.0%)	4 (80.0%)	5 (62.5%)	5 (62.5%)
Progressive disease, n (%)	4 (16.0%)	1 (20.0%)	2 (25.0%)	1 (12.5%)
Not evaluable, n (%)	1 (4.0%)	0	1 (12.5%)	0

Visit cutoff date: 29 June 2018.
Includes patients who had measurable disease at baseline per the investigator and ≥16 weeks of follow-up or who discontinued treatment.
[a]Per modified RECIST/PCWG3 criteria.
[b]One patient had a *BRIP1* alteration and 1 patient had a *FANCA* alteration.
CI, confidence interval; HRR, homologous recombination repair; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 3. Best Change from Baseline in Sum of Target Lesions (n=46)



TOPARP-B: Phase 2 randomized trial with olaparib with DDR alterations

Results: Primary Endpoint Analyses

- 98 randomized, 92 evaluable for primary endpoint analysis (6 found ineligible/not evaluable and excluded as per SAP/IDMC).

	Total (n=92)			Dose group					
				300mg (n=46)			400mg (n=46)		
	resp/n	%	95% CI	resp/n	%	95% CI	resp/n	%	95% CI
Composite Response (confirmed)	**43/92**	**46.7%**	**36.3-57.4**	**18/46**	**39.1%**	**25.1-54.6**	**25/46**	**54.3%**	**39.0-69.1**
RECIST Response	14/70	20.0%	11.4-31.3	6/37	16.2%	6.2-32.0	8/33	24.2%	11.1-42.3
PSA Response ≥50%	30/89	33.7%	24.0-44.5	13/43	30.2%	17.2-46.1	17/46	37.0%	23.2-52.5
CTC conversion	28/55	50.9%	37.1-64.6	13/27	48.1%	28.7-68.1	15/28	53.6%	33.9-72.5
RECIST / PSA response	32/92	34.8%	25.1-45.4	13/46	28.3%	16.0-43.5	19/46	41.3%	27.0-56.8

Per design, ≥19 "composite responses" needed in either arm to recommend dose → 400 mg BID cohort meet threshold → biomarker identified in TOPARP-A is considered validated.

Mateo ASCO 2019

Results: Various DDR

	Group 1: **BRCA1/2 (n=30)**		Group 2: **ATM (n=19)**		Group 3: **CDK12 (n=20)**		Group 4: **PALB2 (n=7)**		Group 5: **Other (n=20)**	
	resp/n	%	resp/n	%	resp/n	%	resp/n	%	resp/n	%
Composite Response (confirmed)	**25/30**	**83.3%**	**7/19**	**36.8%**	**5/20**	**25.0%**	**4/7**	**57.1%**	**4/20**	**20.0%**
RECIST Objective Response	11/21	52.4%	1/12	8.3%	0/18	0.0%	2/6	33.3%	0/17	0.0%
PSA response ≥50%	23/30	76.7%	1/19	5.3%	0/20	0.0%	4/6	66.7%	2/17	11.8%
CTC conversion	17/22	77.3%	5/10	50.0%	5/12	41.7%	0/2	0.0%	3/11	27.3%
RECIST / PSA response	24/30	80.0%	2/19	10.5%	0/20	0.0%	4/7	57.1%	2/20	10.0%

Non-mutually exclusive subgroups - one patient with BRCA1/2+CDK12+Other mutations and two patients with PALB2+Other mutations included in analysis for each subgroup separately.

Other mutations – 4 responders with mutations in: *BRCA2+CDK12+CHEK2* (CTC response), *FANCA* (CTC/PSA response), *WRN* (CTC response), *CHEK2* (PSA response)

Ongoing Trials of PARP Inhibitors in Prostate Cancer

Drug	Phase	Description	NCT #
Rucaparib	2	Rucaparib (TRITON2)	NCT02952534
Rucaparib	3	Rucaparib vs. patient/physician choice (TRITON3)	NCT02975934
Rucaparib	2	Rucaparib for germline HRD metastatic hormone-sensitive prostate cancer (TRIUMPH)	NCT03413995
Rucaparib	2	Rucaparib for non-metastatic hormone-sensitive prostate cancer (ROAR)	NCT03533946
Rucaparib	2	Rucaparib maintenance for mCRPC patients with HRD after induction docetaxel + carboplatin (PLATI-PARP)	NCT03442556
Niraparib	2	Niraparib (GALAHAD)	NCT02854436
Niraparib	3	Niraparib + abiraterone vs. abiraterone (cohort 1 with HRD enrichment only)	NCT03748641
Olaparib	2	Olaparib (TOPARP)	NCT01682772
Olaparib	3	Olaparib vs. enzalutamide or abiraterone acetate (PROfound)	NCT02987543
Olaparib	2	Olaparib vs. abiraterone vs. abiraterone + olaparib (BRCAAway)	NCT03012321
Talazoparib	2	(TALAPRO-1)	NCT03148795

Profound: Olaparib in mCRPC

- **LYNPARZA® (Olaparib) Phase III Profound Trial in HRR* Mutation-Selected Metastatic Castration-Resistant Prostate Cancer Met Primary Endpoint**
- ***AstraZeneca and Merck's LYNPARZA Met the Primary Endpoint of Significantly Increasing the Time Patients Selected for BRCA1/2 or ATM Mutations Live Without Radiographic Disease Progression vs. Standard of Care Treatment (enzalutamide or abiraterone)***

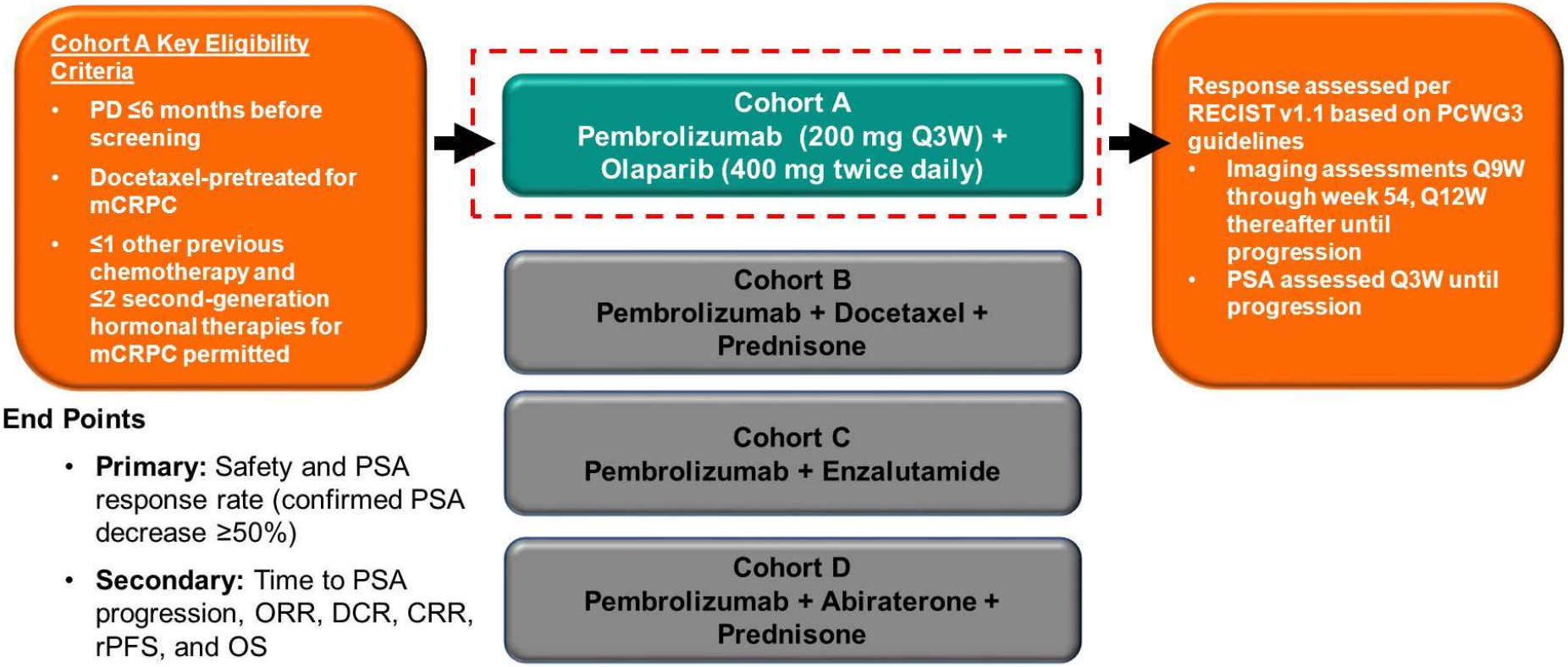
- ***Press Release Aug 7, 2019***

Beyond BRCA

- MSI-H- 3.1%
- CDK12- 6.9%
  - ¾ robust response to CPI

Abida JAMA Onc 2019; Wu Cell 2018

KEYNOTE-365 Study Design (NCT02861573)



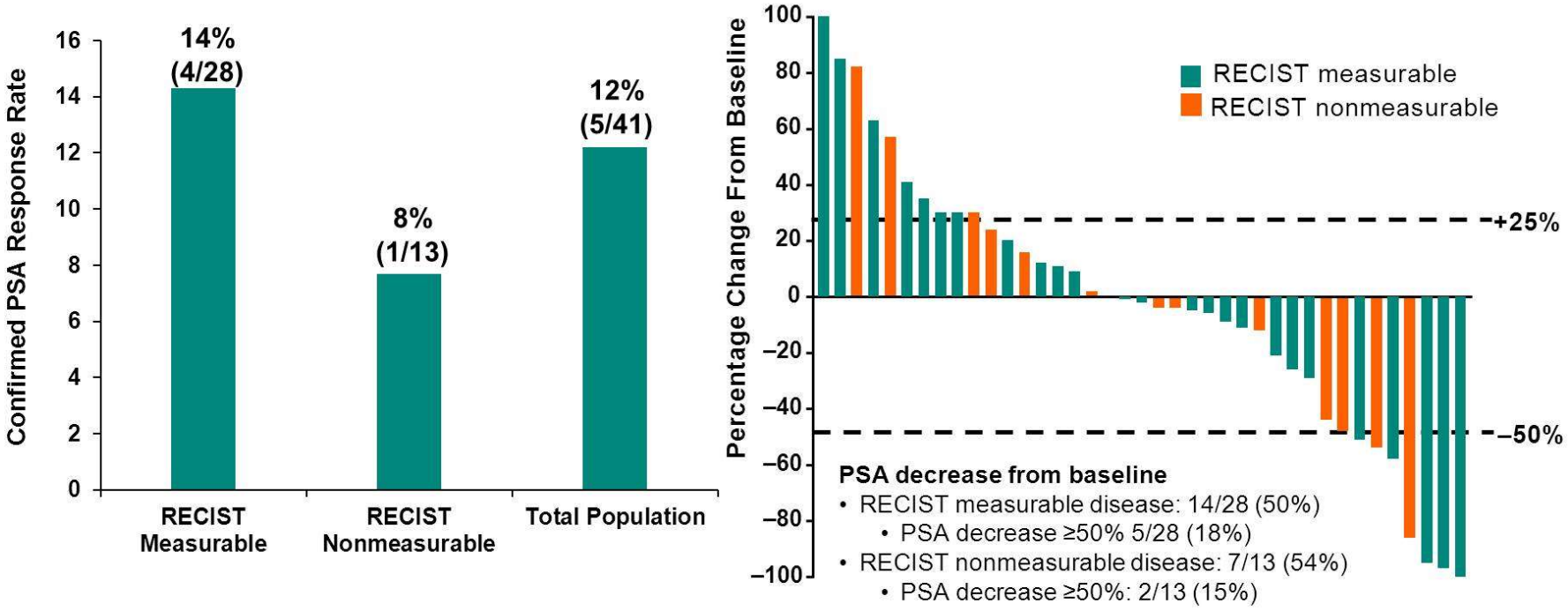
End Points

- **Primary:** Safety and PSA response rate (confirmed PSA decrease ≥50%)
- **Secondary:** Time to PSA progression, ORR, DCR, CRR, rPFS, and OS

Database cutoff: July 27, 2018.

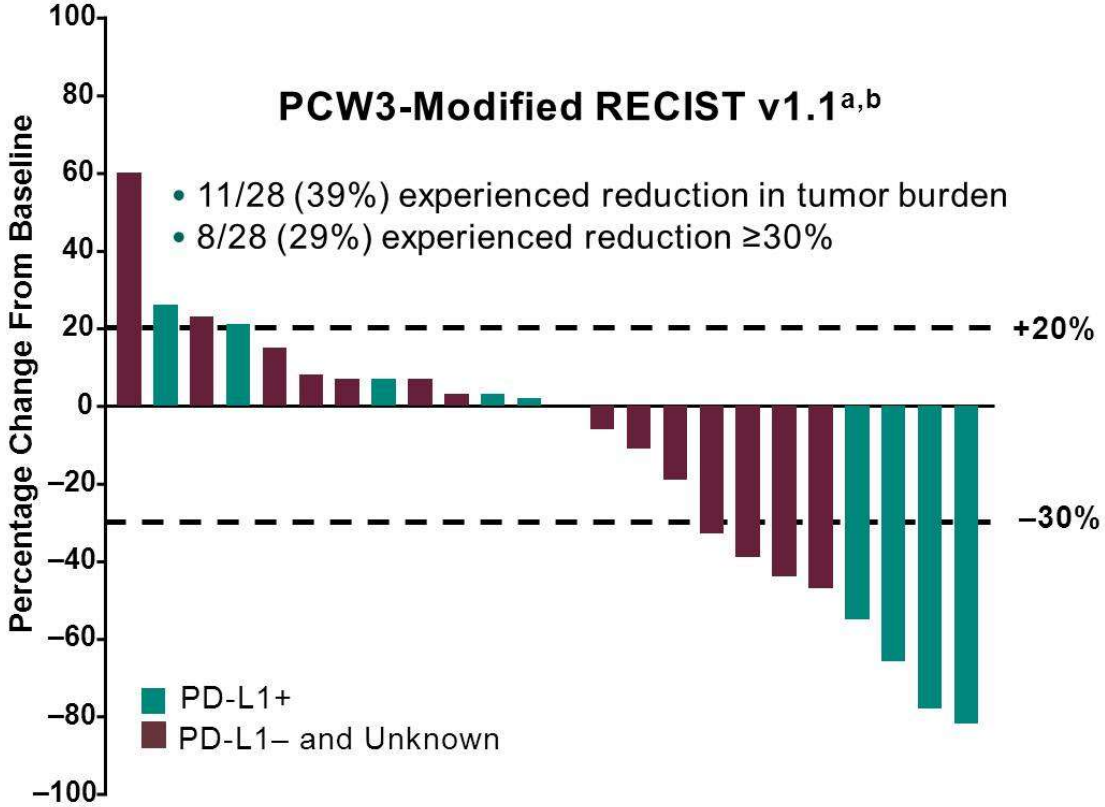
Yu at 2019 ASCO

Confirmed PSA Response Rate and Percentage Change From Baseline[a]



[a]Patients who had a baseline and postbaseline PSA assessment (n = 39). Includes confirmed and unconfirmed PSA decreases from baseline.
Database cutoff: July 27, 2018.

Best Response and Target Lesion Change From Baseline: RECIST-Measurable Disease



Confirmed Response	RECIST-Measurable Disease n = 28
ORR, % (95% CI)	7 (1-23)
DCR ≥6 mo, % (95% CI)	32 (16-52)
Best response, n (%)	
CR	0
PR	2 (7)
SD of any duration	13 (46)
PD	9 (32)
Not evaluable[c]	0
No assessment[d]	4 (14)

[a]Based on investigator assessment. Includes confirmed and unconfirmed responses. [b]Patients who received ≥1 dose of study drug and had a baseline scan and a postbaseline assessment (n = 24). [c]Includes patients who discontinued or died before first postbaseline scan. [d]Includes patients with insufficient data for response assessment.
Database cutoff: July 27, 2018.

Phase II Trial: ^{177}Lu-PSMA-617 in mCRPC With Progression on Standard Treatment

- N = 30 men with mCRPC, PD on SoC agents, and high PSMA expression treated at Peter MacCallum Cancer Centre, in Melbourne, Australia
- Treatment: 1-4 cycles IV ^{177}Lu-PSMA-617 once weekly for 6 weeks
- Primary endpoints
  - PSA response (defined as > 50% decline from baseline)
  - Toxicity (per CTCAE)
  - Imaging responses (bone scan, CT, PSMA, FDG PET/CT)
  - QoL (EORTC-Q30 and BPI short form questionnaires, measured up to 3 mos following treatment)

Hofman MS,et al. Lancet Oncol. 2018.

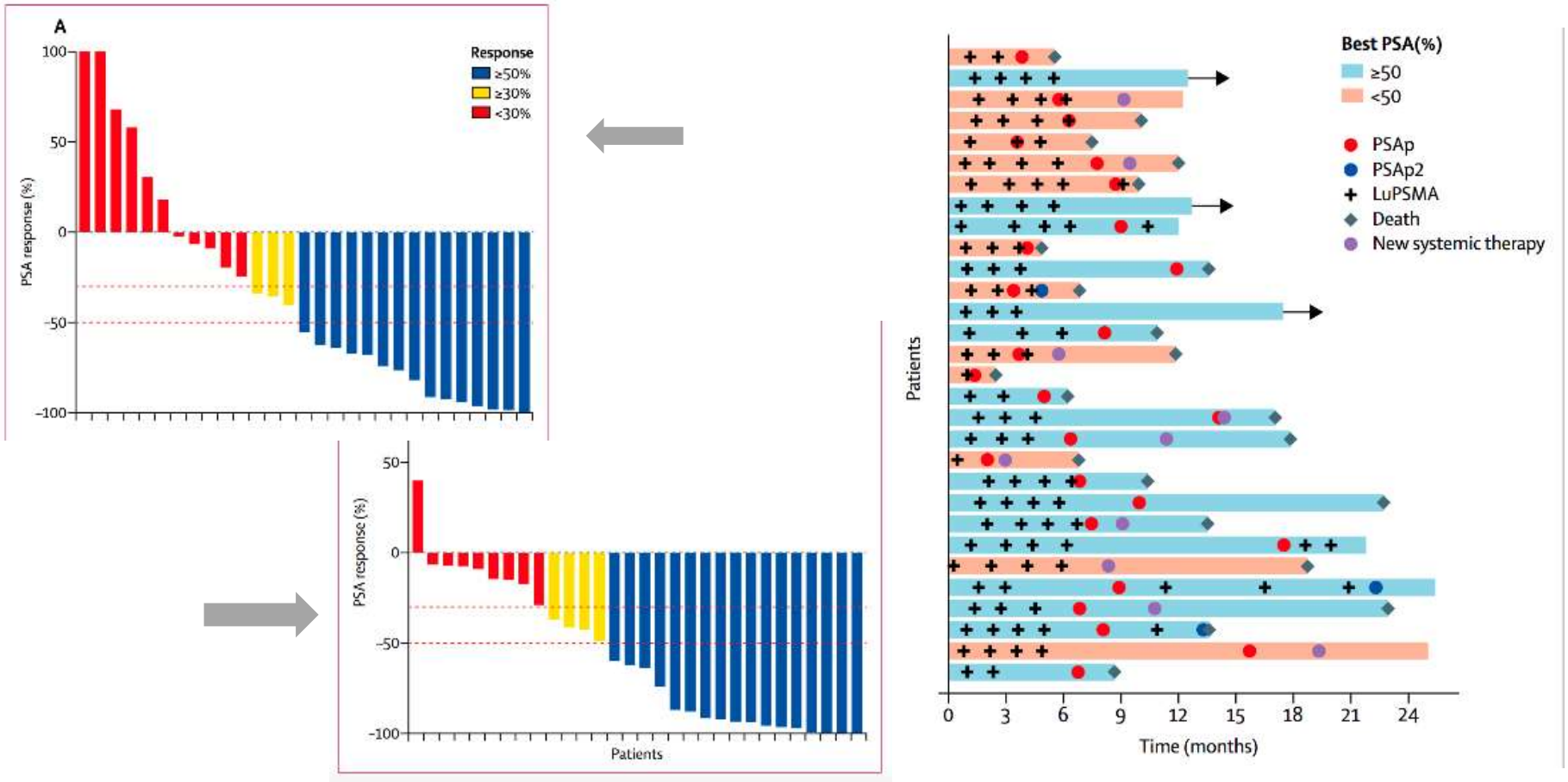
^{177}Lu-PSMA-617 in Progressive mCRPC: Baseline Characteristics

Characteristic	N = 30
Median age, yrs (range)	71 (67-75)
Median time since PC diag, yrs (range)	9 (5-13)
Median Gleason score at diag (range)	8 (7-9)
Median alk phos, U/L (range)	117.5 (80.8-184.5)
Hemoglobin, g/L	118 (103-127)
LDH, U/L (range)	247 (209-304)
Median PSA, µg/L (range)	189.8 (80.1-372.0)
PSADT, µg/L per mo (range)	2.4 (1.4-3.5)
ECOG PS, n (%)	
▪ 0	11 (37)
▪ 1	14 (47)
▪ 2	5 (17)

Characteristic	N = 30
No. of prior chemo regimens, n (%)	
▪ 1	12 (40)
▪ 2	12 (40)
▪ ≥ 3	2 (7)
Previous treatment, n (%)	
▪ Abiraterone, enzalutamide, or both	25 (83)
▪ Docetaxel	24 (80)
▪ Cabazitaxel	14 (47)
▪ Palliative radiotherapy	14 (47)
▪ Bisphosphonate or denosumab	22 (73)
Site of disease (PSMA-PET), n (%)	
▪ Bone	29 (97)
▪ Nodal	24 (80)
▪ Visceral	4 (13)

Hofman MS, et al. Lancet Oncol. 2018

^{177}Lu-PSMA-617 in Progressive mCRPC: Clinical Responses



Hofman MS, et al. Lancet Oncol. 2018.

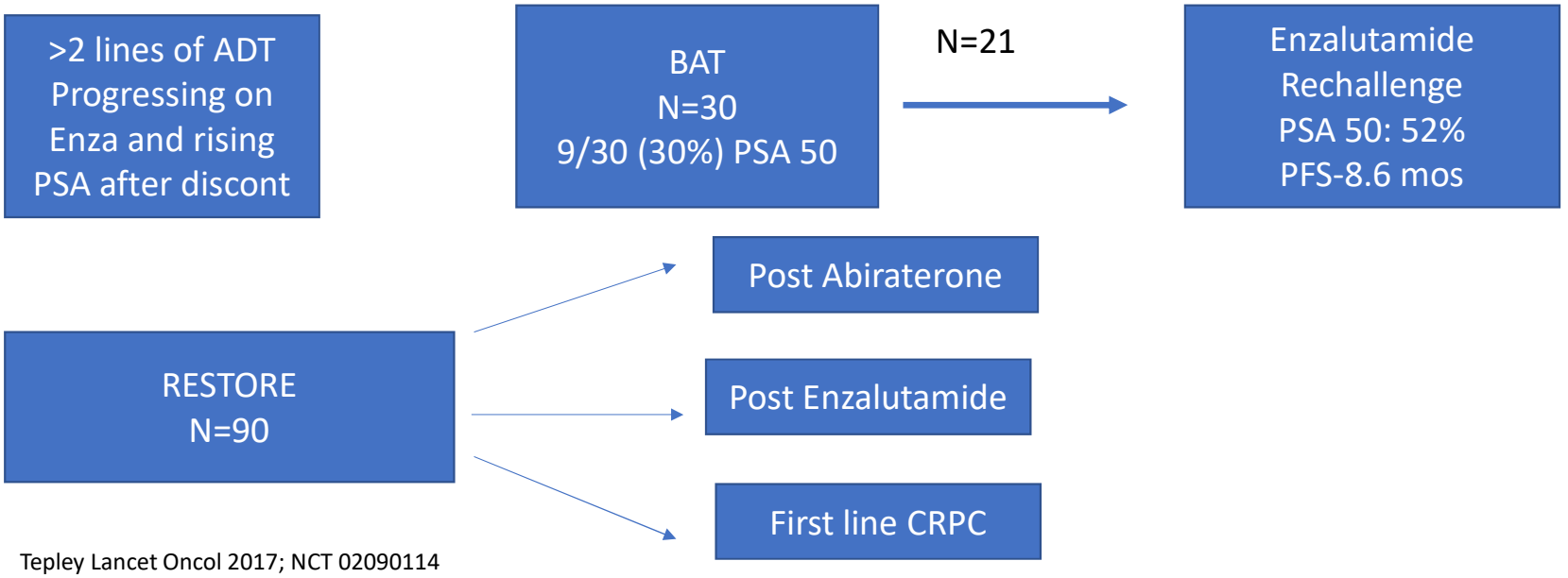
^{177}Lu-PSMA-617 in Progressive mCRPC: Toxicities

	Grade 1–2	Grade 3	Grade 4	Grade 1–2, attributed to LuPSMA*	Grade 3 attributed to LuPSMA*	Grade 4 attributed to LuPSMA*
Dry mouth	26 (87%)	0	0	26 (87%)	0	0
Lymphocytopenia	12 (40%)	13 (43%)	0	11 (37%)	11 (37%)	0
Thrombocytopenia	12 (40%)	5 (17%)	3 (10%)	8 (27%)	3 (10%)	1 (3%)
Fatigue	16 (53%)	1 (3%)	0	15 (50%)	0	0
Nausea	15 (50%)	0	0	15 (50%)	0	0
Anaemia	7 (23%)	7 (23%)	0	4 (13%)	4 (13%)	0
Neutropenia	12 (40%)	2 (7%)	0	8 (27%)	2 (7%)	0
Pain	8 (27%)	3 (10%)	0	5 (17%)	1 (3%)	0
Vomiting	10 (33%)	0	0	10 (33%)	0	0
Anorexia	8 (27%)	0	0	7 (23%)	0	0
Dry eyes	5 (17%)	0	0	5 (17%)	0	0
Weight loss	3 (10%)	0	0	3 (10%)	0	0
Disseminated intravascular coagulation	0	1 (3%)	0	0	0	0
Oculomotor nerve disorder	1 (3%)	0	0	1 (3%)	0	0
Spinal fracture	0	1 (3%)	0	0	0	0
Hip fracture	0	1 (3%)	0	0	0	0

Hofman MS, et al. Lancet Oncol. 2018

Bipolar Androgen Therapy- BAT

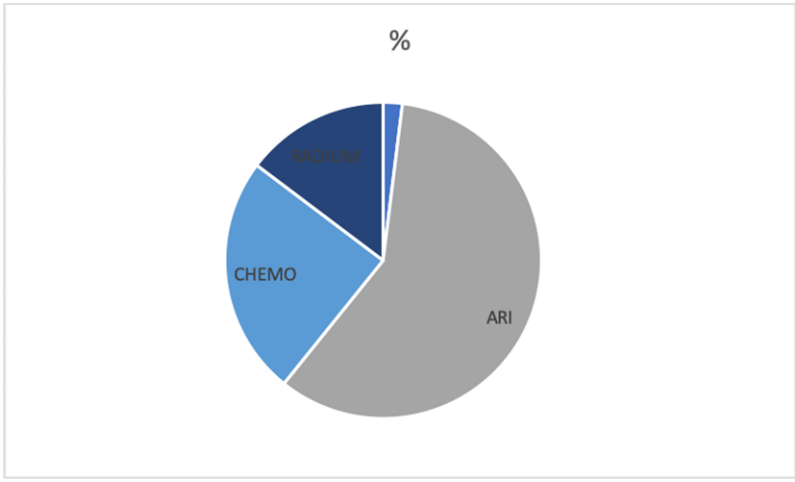
- Alternating high doses of Testosterone with castrate levels : dsDNA breaks

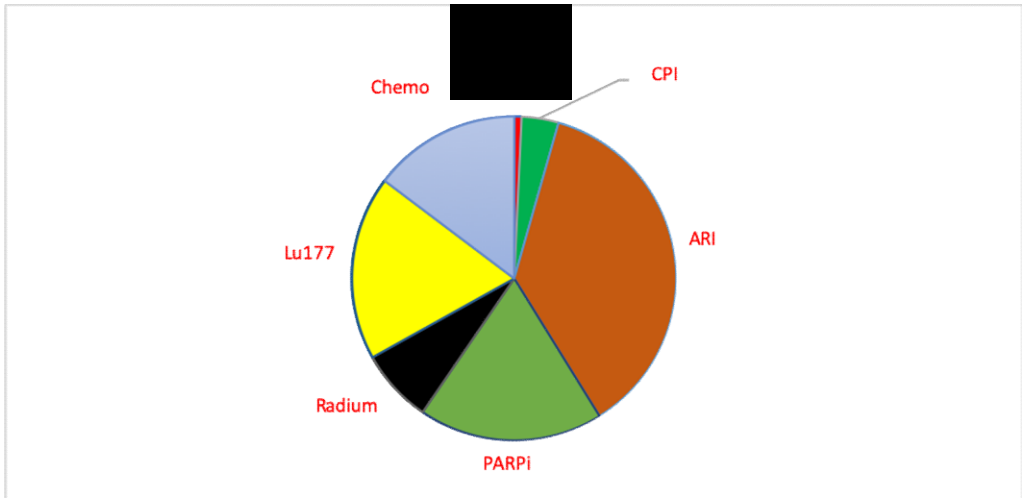


Tepley Lancet Oncol 2017; NCT 02090114

Conclusion

- mCRPC is an unmet need
- Need new class of drugs that are non cross resistant with the current ones
- Optimum sequence unknown
- Delay time between drugs of similar class
- Promising drugs : PARPi, Radio ligands, immunotherapeutics





Questions? Thank You

@sandysrimd