MODULE 3: Genitourinary Cancers

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Questions

- 1. What is your current approach to endocrine therapy (in addition to radiation therapy) for locally advanced prostate cancer?
- 2. How do you select among enzalutamide, apalutamide and darolutamide for your patients with nonmetastatic castration-resistant prostate cancer? Have you or would you use abiraterone in this setting?
- 3. What is the optimal therapeutic approach for a patient with metastatic hormone-sensitive prostate cancer, and how does this vary based on disease volume and symptomatology?
- 4. In general, when do you believe ^{177}Lu-PSMA-617 should be introduced into treatment for patients with metastatic castration-resistant prostate cancer (mCRPC), and how do you sequence this strategy relative to other evidence-based options? What side effects/tolerability issues are associated with this agent?
- 5. Which patients with mCRPC should undergo genetic testing, and what type (eg, germline versus somatic, panel versus one-off)? How should PARP inhibitors be incorporated into the treatment of patients with and without documented homologous recombination repair (HRR) gene mutations? Would you combine one of these agents with an AR pathway inhibitor for a patient with or without an HRR abnormality outside of a trial?

Discussion Question

What is your current approach to endocrine therapy for locally advanced prostate cancer, in addition to radiation therapy?

Endocrine Rx for Locally Advanced PC

- Primary:
  - NCCN low risk: none; Intermediate favorable none; intermediate unfavorable- 6 mos; high risk- 1.5 years; Very high risk: ADT/abiraterone for 1.5-2 years; Node positive- ADT/abiraterone 1.5-2 years

- Salvage
  - SOC- 6 months- ADT GETUG-16
  - Controversial about duration and what the agent should be
  - None vs 6 months vs 1.5-2 yrs
  - Strategies for escalation/de-escalation ongoing

Discussion Question

How do you select among enzalutamide, apalutamide and darolutamide for your patients with nonmetastatic castration-resistant prostate cancer (CRPC)? Have you used or would you use abiraterone in this setting?

nmCRPC: PROSPER/SPARTAN/ARAMIS: Results

Characteristic	PROSPER		SPARTAN		ARAMIS	
	Enzalutamide + ADT (n = 933)	Placebo + ADT (n = 468)	Apalutamide + ADT (n = 806)	Placebo + ADT (n = 401)	Darolutamide + ADT N=955	Placebo +ADT N=554
MFS, mos	**36.6**	14.7 HR-0.29	**40.5**	16.2 HR 0.28	**40.4**	18.4 HR 0.41
OS, mos	67	56.3	73.9	59.9 HR 0.78	NR	NR HR 0.69
▪ PSA progression ▪ (mos)	**37.2**	3.9 HR 0.07	40.5	3.7 HR 0.07	**33.2**	7.3 HR 0.13

Safety	**SPARTAN**		**PROSPER**		**ARAMIS**	
	APA (n = 803)	**PBO (n = 398)**	**ENZA (n = 930)**	**PBO (n = 465)**	**DARO (n = 954)**	**PBO (n = 554)**
Any AEs, n (%)	781 (97.0)	373 (94.0)	876 (94)	380 (82)	794 (83.2)	426 (76.9)
Any serious AEs, n (%)	290 (36.0)	99 (25.0)	372 (40)	100 (22)	237 (24.8)	111 (20.0)
AEs leading to discontinuation, %	15.0	7.3	17.0	9.0	8.9	8.7
AEs (all grades), %						
Fatigue	33.0	21.0	46.0	22.0	13.2	8.3
Hypertension	28.0	21.0	18.0	6.0	7.8	6.5
Rash	26.0	6.3	4.0	3.0	3.1	1.1
Falls	22.0	9.5	18.0	5.0	5.2	4.9
Fractures	18.0	7.5	18.0	6.0	5.5	3.6
Mental impairment disorders	5.1	3.0	8.0	2.0	2.0	1.8

Hussain NEJM 2018; Sternberg NEJM 2020; Smith NEJM 2018; Smith Eur Urol 2021; Fizazi NEJM 2019; Fiazi NEJM 2020.

nmCRPC

- Abiraterone
- IMAAGEN study: 131 pts
- PSA ≥50% reduction = 87%
- No level 1 evidence

Ryan CJ J Urol 2018

Discussion Question

What is the optimal therapeutic approach for a patient with metastatic hormone-sensitive prostate cancer, and how does this vary with disease volume and symptomatology?

RTP
RESEARCH
TO PRACTICE

Choices in mHSPC

- ADT is the backbone for the treatment of mHSPC
- Adding either docetaxel or abiraterone improved OS by 30%
- Benefit of docetaxel clear in high volume vs low volume disease
- Debate over docetaxel vs abiraterone: multiple choices; efficacy the same
- ARI: apalutamide/Enzalutamide superior to ADT alone
- Triple Rx: PEACE 1: ADT + Docetaxel + Abiraterone >ADT + Docetaxel
- ARASENS: ADT + Docetaxel + Darolutamide > ADT + Docetaxel
- Selection of Rx: High volume vs low volume; de novo vs metachronous; chemo fitness; frailty; co-morbidities; # HTN meds; cardiac health; support @home

mHSPC trials

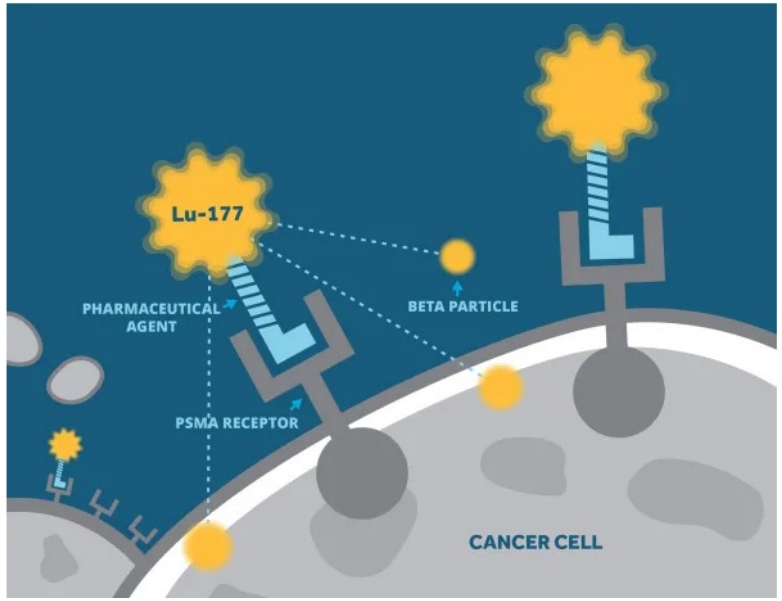
Trial Name	Experimental arm	Comparator arm	rPFS	OS
CHAARTED [1]	Docetaxel	ADT	--	HR: 0.72; 57.6 vs 44 mos
STAMPEDE–C [2]	Docetaxel	ADT	--	HR: 0.81; 59.1 vs 43.1 mos
LATITUDE [3]	Abiraterone	ADT	33 v 14.8 mos HR 0.47	HR: 0.66; 53 vs 36 mos
STAMPEDE-G [4]	Abiraterone	ADT	--	HR :0.6; 79 vs 46 mos
ARCHES [5]	Enzalutamide	ADT	HR: 0.39 NR vs 19	HR: 0.66; NR vs NR
ENZAMET [6]	Enzalutamide	ADT+NSAA With docetaxel	HR-0.34 HR: 0.48	HR- 0.53 HR: 90
TITAN [7]	Apalutamide	ADT	HR- 0.48	HR: 0.65 NR vs 52.2
PEACE-1 [8]	Abiraterone	ADT+Docetaxel	4.5 yrs vs 2 HR-0.5	HR: 0.75
ARASENS [9]	Darolutamide	ADT+Docetaxel	NR	HR: 0.68; NR vs 48.9 mos

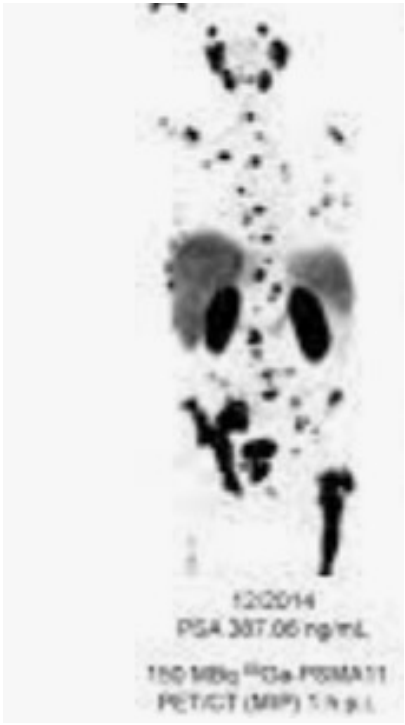
1.Sweeney C NEJM 2015; Kyriakopoulos J Clin Oncol 2018 2.Clarke N Ann Oncol 2019;3. Fizazi K Lancet Oncol 2019; 4.James ND Intl J Cancer 2022; 5.Armstrong A J Clin Oncol 2019. Armstrong AJ J Clin Oncol 2022; 6.Davis NEJM 2019; 7.Chi KN NEJM 2019; Chi KN J Clin Oncol 2021 8.Fizazi Lancet 2022; 9.Smith MR NEJM 2022

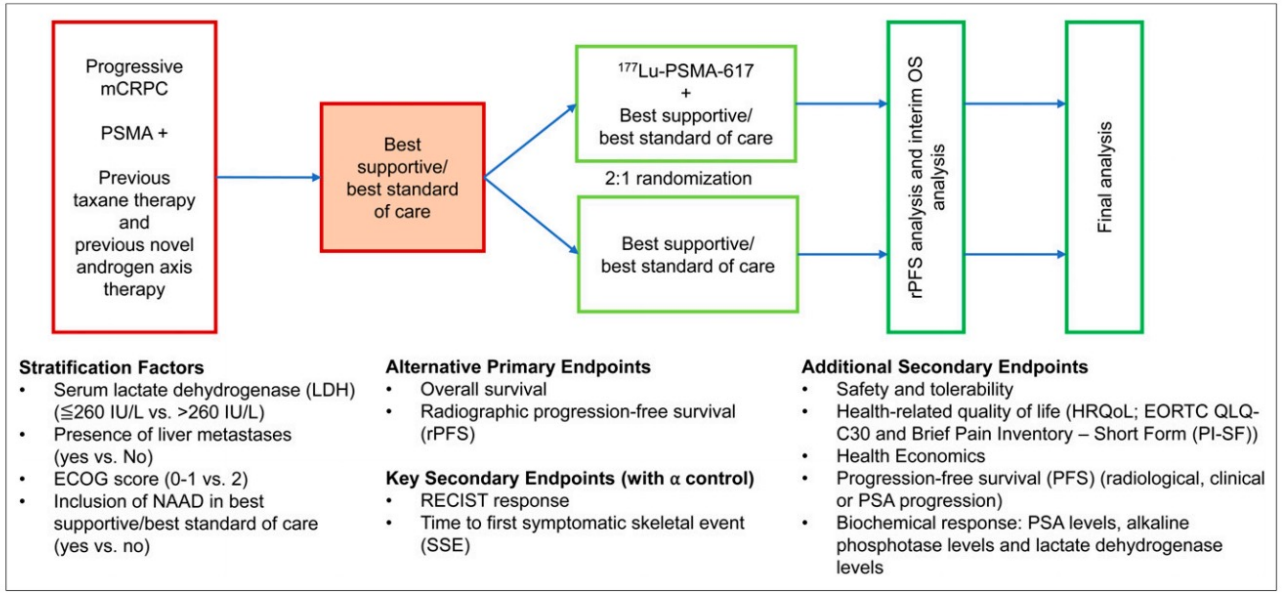
Discussion Question

In general, when do you believe ^{177}Lu-PSMA-617 should be introduced into treatment for patients with metastatic CRPC (mCRPC), and how do you sequence this strategy relative to other evidence-based options? What side effects or tolerability issues are associated with this agent?

VISION: Phase 3 randomized study Lu177







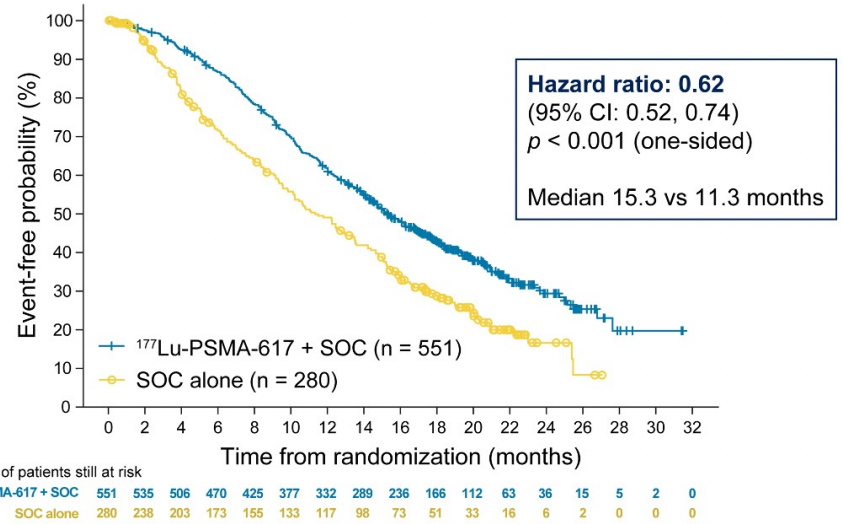
Sartor NEJM 2021

Chalk Talk – Sandy Srinivas, MD

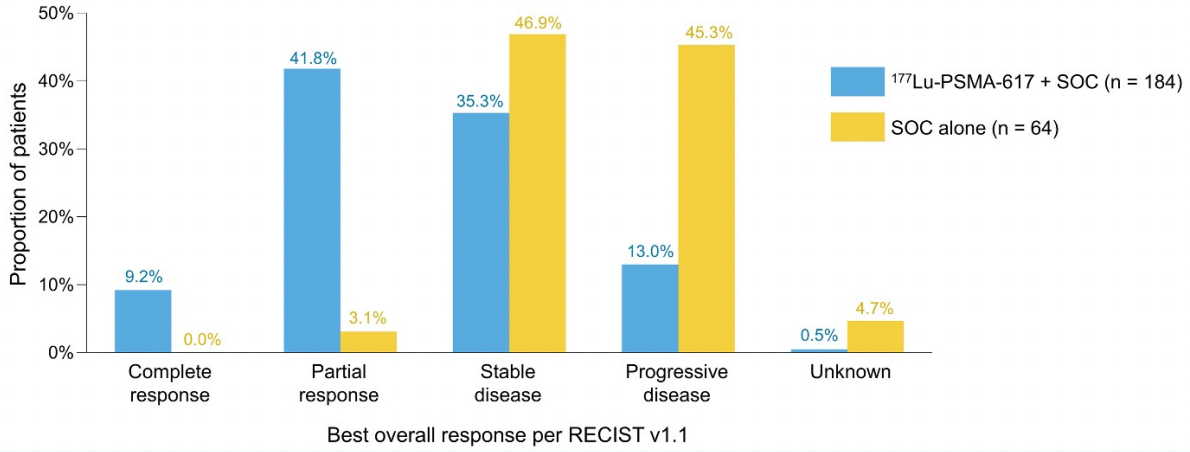
Improvement in Longevity:

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

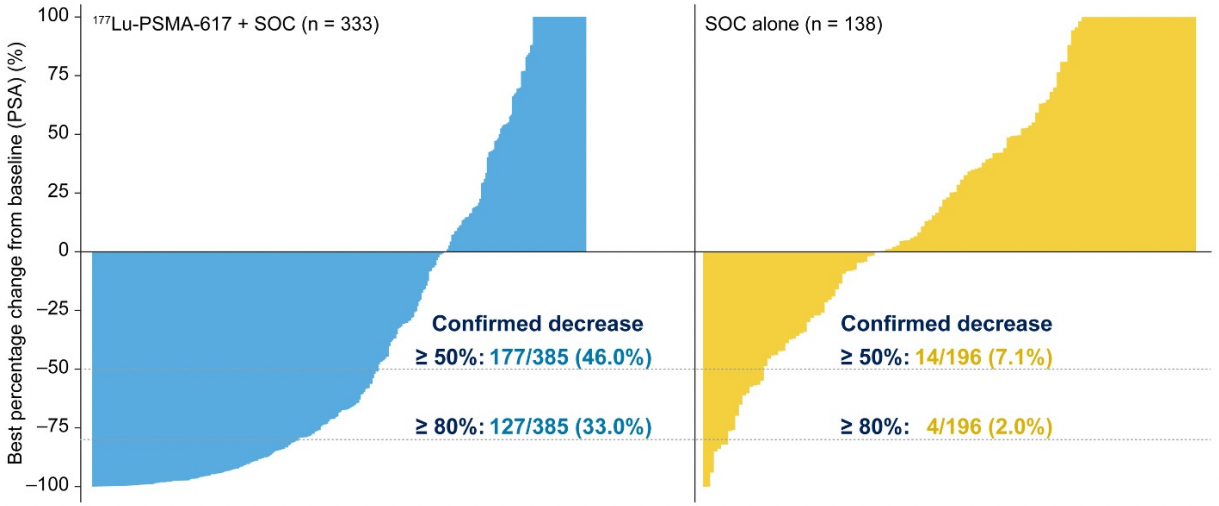
Primary analysis
All randomized patients
(N = 831)



Secondary endpoint: RECIST v1.1 responses favored the ^{177}Lu-PSMA-617 arm in patients with measurable disease



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



Morris ASCO 2021; Sartor NEJM 2021

Treatment-Emergent Adverse Events of Interest

Patients with TEAEs of interest[a]	FAS safety set (N = 734)			
	All grades		Grade 3–5[b]	
	^{177}Lu-PSMA-617 + BSoC (n = 529) n (%)	BSoC only (n = 205) n (%)	^{177}Lu-PSMA-617 + BSoC (n = 529) n (%)	BSoC only (n = 205) n (%)
Fatigue (including asthenia)	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)
Months of exposure – median (range)	^{177}Lu-PSMA-617 + BSoC (n = 529)		BSoC only (n = 205)	
BSoC	7.56 (0.3–31.3)		2.07 (0.0–26.0)	
^{177}Lu-PSMA-617	6.90 (0.3–10.2)		-	

BSoC, best standard of care; FAS, full analysis set; TEAE, treatment-emergent adverse event.
[a]Randomized treatment-emergent safety topics were defined as any safety topic that occurred on or after start of randomized treatment up to 30 days after last administration of randomized treatment or prior to the initiation of subsequent anticancer treatment.
[b]Patients with multiple grades for a safety topic are only counted under the maximum grade.
Reference: Sartor O et al. *N Engl J Med*. 2021;385(12):1091-1103.

Discussion Question

Which patients with mCRPC should undergo genetic testing, and what type (eg, germline versus somatic, panel versus one-off)? How should PARP inhibitors be incorporated into therapy for patients with and without documented homologous recombination repair (HRR) gene mutations? Would you combine one of these agents with an AR (androgen receptor) pathway inhibitor for a patient with or without an HRR abnormality outside of a trial?

BRCA +/mCRPC

- Testing done in all newly dx mHSPC; mCRPC
- Olaparib approved pre-docetaxel: PROfound study: rPFS in cohort A: 7.4 vs 3.6 mos; OS- 19.1 vs 14.7 mos
- Rucaparib approved post NHT and docetaxel: TRITON2:ORR of 43.5%

- Recent data :
- Magnitude: Niraparib+ Abiraterone vs Placebo +abiraterone
- HRRm+: Niraparib +Abiraterone improved rPFS:0.73; 16.5 vs 13.7 mos; HRRm-:Neg
- PROpel: Olaparib+Abiraterone vs Placebo +abiraterone
- rPFS: 24.8 vs 16.6 mos; HR-0.66; HRRm+: HR-0.5; HRRm-: HR- 0.76

De Bono NEJM 2020; Hussain NEJM 2020; Abida J Clin Oncol 2020; Chi K J clin Oncol 2022; Clarke NEJM Evidence 2022