INTEGRATING PSMA PET SCAN INTO THE MANAGEMENT OF PROSTATE CANCER

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STUDY OBJECTIVES

1. Recognize the indication for prostatespecific membrane antigen (PSMA) PET scans in clinical practice

2. Discuss strategies to integrate PSMA PET scans into clinical practice

DISCLOSURE

The use of brand names are included for learning purposes only

Dr. Zhang has received honorarium for participating in advisory board and speaker programs from AstraZeneca, Bayer, Dendreon, Pfizer, Seagen, and Sanofi in the past 24 months.

Gigi Jameel has received speaker fees from Sanofi

WHICH OF THE FOLLOWING IS **NOT** TRUE ABOUT PSMA PET IN PROSTATE CANCER MANAGEMENT?

A) It is indicated to stage high risk prostate cancer

B) It is a staging tool for patients with rising PSA after radical prostatectomy for prostate cancer

C) It is a staging tool for patients with rising PSA after initial definitive radiation for prostate cancer

D) Patients with negative PSMA PET will not benefit from ¹⁷⁷Lu-PSMA-617

E) There are established guidelines on how to use PSMA PET to assess response to treatments

INDICATION#1: STAGING HIGH RISK PROSTATE ADENOCARCINOMA

A 63 yo male who was found to have a PSA of 33 and positive DRE during routine screening. Subsequent prostate biopsy revealed bilateral Gleason 9 (4+5) prostate adenocarcinoma. Left seminal vesicle invasion was also noted on prostate MRI.

Ga 68 PSMA PET scan reported increased uptakes in prostate gland along with a 12 mm left pelvic LN with SUV max of 26.

What's your treatment recommendation:

- A) Start combined ADT with leuprolide and apalutamide for stage IV T3bN1M0 prostate cancer
- B) Radical prostatectomy with pelvic LN dissection
- C) Start combined ADT with leuprolide plus abiraterone plus prednisone, followed by definitive XRT to the prostate gland



STAMPEDE: ABI W OR WO ENZA +ADT XRT VS ADT XRT FOR MO HIGH RISK PROSTATE CA

M0 on conventional imaging, and were either node positive or, if node negative, were either high risk (defined as having at least two of the following: T3 or T4, Gleason 8–10, and PSA ≥40) or relapsing with high-risk features

Local radiotherapy (74 Gy in 37 fractions to the prostate and seminal vesicles or the equivalent using hypofractionated schedules) was mandated for node negative and encouraged for node positive disease.

ADT was given for 3 years and combination therapy for 2 years, except if local radiotherapy was omitted when treatment could be delivered until progression.

Attard et al Lancet 2022

FOREST PLOT ON METASTASIS FREE SURVIVAL

	SOC	SOC plus abiraterone and prednisolone with or without enzalutamide	HR (95% CI)	P _{interaction}
	Number of events/ number of patients	Number of events/ number of patients		
Nodal status				0.22
NO	140/598	89/599	0-60 (0-46-0-78)	
N+	165/389	91/385	0.49 (0.38-0.64)	
Age at randomisation, years				0.64
<70	177/576	106/575	0.52 (0.41-0.66)	
≥70	129/412	74/411	0.55 (0.41-0.73)	
WHO performance status at rand	omisation			0.00656
0	257/810	139/711	0-47 (0-38-0-58)	
1-2	49/178	49/187	• 0.86 (0.58-1.28)	
Regular NSAID or aspirin use at ba	aseline		1 ECO 11	0.0052
No	224/772	148/762	0-62 (0.51-0.77)	
Yes	82/216	32/224	0.32 (0.21-0.48)	
Radiotherapy planned as part of 9	SOC			0.67
No	68/145	41/145	0.51 (0.34-0.76)	
Yes	238/843	139/841	0-54 (0-44-0-67)	
Overall		•	0.53 (0.45-0.64)	
		0-25	1 4	
et al Lancet 2022		Favours combination thera	→ → · · · · · · · · · · · · · · · · · ·	



SUMMARY OF STAMPEDE MO HIGH RISK PROSTATE CA

- Addition of 2 years of abiraterone to ADT in men with high-risk M0 prostate cancer significantly improved metastasis-free and overall survival.
- The addition of enzalutamide to abiraterone does not appear justified as additional toxicity and cost come with no evidence of a difference in treatment effect.
- M0 patients relapsing after previous treatment were under-represented
- Abiraterone for 2 years should now be considered a standard treatment option in addition to 3-year ADT for newly diagnosed prostate cancer with high-risk features (particularly N1M0 prostate ca).

INDICATION#2: STAGING IN BIOCHEMICAL RECURRENCE FOR PATIENTS WHO ARE INTERESTED IN LOCAL SALVAGE/ABLATIVE TX

1/2011, Radical prostatectomy with pelvic lymph node sampling for Gleason 9 (4+5) pT3aN0Mx prostate ca with post OP PSA of 0.015

3/2014, salvage radiation to the prostatic bed after PSA increased to 0.22.

PSA 0.2 in 2016, 2.4 in 2019, 4.03 in 3/2019

8/20/19, selected removal of Fluciclovine PET positive pelvic LN in Germany with pathology confirmed pN1 metastatic prostate adenocarcinoma. *NGS test was only notable for SPOP mutation*

PSA 1.9 in 10/2019, 3.2 in 1/2020, continues to decline systemic therapy

3/3/2020, stereotactic XRT to the retroperitoneal LN 35 Gy in 5 fractions with PSA 5.1 in 7/2020

10/27/20, PSMA PET guided left cervical LN dissection in Germany with removal of 6 LNs and 4 were + for prostate ca at age 82. PSA slightly decline from 5.1 in 7/2020 to 4.1 in 12/2020.

PSA 7.3 in 5/2021, 9.5 in 1/2022 & 13.6 in 5/2022

11/2022, PSMA PET with supraclavicular lymphadenopathy and retroperitoneal lymphadenopathy. 12/2022: 17.1- began treatment with relugolix with latest PSA of 2.43 in 3/2023.

INDICATION #3: SELECTING M1 CRPC FOR ¹⁷⁷LU-PSMA-617(PLUVICTO)

VISION: phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC)



Stratification Factors

- Serum lactate dehydrogenase (LDH) (<260 IU/L vs. >260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

Alternate Primary Endpoints

- Overall survival
- Radiographic progression-free survival (rPFS)

Key Secondary Endpoints (with a control)

- RECIST response
- Time to first symptomatic skeletal event (SSE)

Additional Secondary Endpoints

- · Safety and tolerability
- Health-related quality of life (HRQoL; EORTC QLQ-C30 and Brief Pain Inventory – Short Form (PI-SF))
- Health economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphatase levels and lactate dehydrogenase levels

DEFINITION OF POSITIVE GALLIUM-68 (⁶⁸GA)–PSMA PET–CT

- PSMA-positive lesions: ⁶⁸Ga-PSMA-11 uptake > liver parenchyma in one or more meta-static lesions of any size in any organ system.
- PSMA-negative lesions: PSMA uptake ≤ liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis.
- Patients with any PSMA-negative metastatic lesion meeting these criteria were ineligible. 126/1003 (12.6%) consented end stage mCRPC patients didn't meet PSMA PET imaging criteria (with either no PSMA-positive lesions or ≥1 exclusionary PSMA-negative lesions).

SELECTED PATIENT CHARACTERISTICS OF VISION TRIAL

	Lung met	Liver met	LN met	Bone met	1 NHA	2 NHAs	>2 NHAs	docetaxel	2 taxanes
Lu177-PSMA	49 (8.9)	63	274	504	298	213	40	534	220
N=551		(11.4)	(49.7)	(91.5)	(54.1)	(38.7)	(7.3)	(96.9)	(39.9)
SOC	28 (10)	38	141	256	128	128	24	273	122
N=280		(13.6)	(50.4)	(91.4)	(45.7)	(45.7)	(8.6)	(97.5)	(43.6)

¹⁷⁷Lu-PSMA-617 improved rPFS and OS for mCRPC in the post docetaxel setting



¹⁷⁷Lu-PSMA-617 treatment emergent adverse events

	All gr	ades	Grade 3–5		
Patients, n (%)	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	
Fatigue	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 Lymphopenia Anemia Thrombocytopenia	66 (12.5) 75 (14.2) 168 (31.8) 91 (17.2)	4 (2.0) 8 (3.9) 27 (13.2) 9 (4.4)	13 (2.5) 41 (7.8) 68 (12.9) 42 (7.9)	1 (0.5) 1 (0.5) 10 (4.9) 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)	

CASE 3: 57 YO WITH DE NOVO M1 PROSTATE CA TO LIVER

12/2018, PSA 75 at screening, staging w/u was notable for liver and bone mets, liver biopsy confirmed prostate adenocarcinoma.

NGS HRR wt, TMB low, MSS stable.

1/2019 – present, continuous leuprolide

2/2019-5/2019, upfront docetaxel x 6

2/21/2020 - 4/2021, enzalutamide for mCRPC, pre-enzalutamide PSA of 38, and PSA nadir of 1.38 on 7/7/20, PSA 21.3 on 3/10/21. Scans showed overall stable liver and bone mets.

What are his risk features? What Tx would you recommend?

- A) Abiraterone plus prednisone
- B) Cabazitaxel
- C) Cabazitaxel plus Carboplatin
- D) Sipuleucel-T
- E) Radium 223

CASE 3: PROGRESS TO M1 CRPC 9 MONTHS POST UPFRONT DOCETAXEL

5/20/2021 – 3/2022, Phase II trial of AZD4635 in Combination with Cabazitaxel and Durvalumab

7/22/21 - Grade 3 lipase elevation, cabazitaxel only

 $8/13/21-11/29/21,\,AZD4635$ level -1, durvalumab and cabazitaxel

12/2021 - 2/2022, AZD4635 level -1 + durvalumab 3/2022: XRT to L3/L4 met with anterior epidural extension Rising PSA from 16.57 in 2/2022 to 37.92 in 5/2022

5/2022, 18F-DCFPyL PSMA PET



left superior hila node (SUVmax 9.1), left adrenal gland (SUVmax 15.6), Numerous avid sclerotic skeletal mets

18F-DCFPYL PSMA PET IN 5/2022

7/8/22, ¹⁷⁷Lu-PSMA-617 dose 1 with pre tx PSA of 18.88 8/30/22, XRT for right hip with PSA of 40.6 10/28/22, ¹⁷⁷Lu-PSMA-617 dose 2 12/2/022, PSA 542.6, CTC 250, progressive bone mets, d/c pluvicto 1/3/23, PSA 829.76, XRT for spinal cord compression 2/7/23, DOD



ASSOCIATION BETWEEN PSA DECLINE AND RPFS AND OS IN THE 177LU-PSMA-617 ARM OF THE VISION TRIAL



Annals of Oncology (2022) 33 (suppl_7): S616-S652 10.1016/annonc/annonc1070

Case 4: 71 yo with mCRPC and lack of response to abiraterone

1/2010, prostatectomy for Gleason 7(4+3) pT3aN0Mx prostate adenocarcinoma.
2012, salvage intensity modulated radiation therapy/IMRT to the prostatic bed.
2016, started continuous Leuprolide for biochemical recurrence
4/2017 - 10/2017, bicalutamide was added for M0 CRPC

3/2018 – 8/2018, Abiraterone plus prednisone for M1b CRPC, with no PSA response and 2 new lesions were noted in the bone in 7/2018.

2/2019, 2nd opinion at Moffitt with <u>progressive bone mets</u> and PSA of 21.47 while on leuprolide monotherapy. No extraosseous malignancy was identified on outside Fluciclovine PET. Given he is feeling well, he does not want chemotherapy.

What would you recommend?

A) Enzalutamide
B) Radium 223
C) Sipuleucel-T + enzalutamide
D) NGS test with foundation one liquid or Guardant 360



Case 4: Post Abiraterone Treatments for M1 CRPC

He elected to radium 223 and completed 6 doses in 9/2021 with reduction in ALKP, slow ring PSA and stable disease on scans.

Foundation liquid: KLH6 S306L (47.8%), TP53R213* (1.6%), PTEN M199del (0.57%), AR amplification equivocal, TMB 4/Mb, MSS

10/2019 – 4/2020, enzalutamide locally

- 5/2020 10/2021, 10 cycles of docetaxel followed by cabazitaxel locally
- 11/2021, referred back to Moffitt with progressive cancer in the liver and bone
- phase 1/2 study with Regeneron's bispecific T-cell engager, RGN5678/ plus cemiplimab trial.

2/8/22, Received first lead-in dose of REGN5678/ anti-PSAMxCD28 on 2/08/22. Cycle 1, day 1 of REGN5678 with cemiplimab/anti-PD1 on 2/28/22.

6/6/2022, last dose of REGN 5678, with partial response in liver mets, and > 95% PSA reductions (nadir of 8/23 on 7/6/22). Off study due to aseptic encephalitis

11/3/22 – present, ¹⁷⁷Lu-PSMA-617 started for rising PSA and progressive bone mets and pre Tx PSA of 33.3

Neither REGN5678 nor Cemiplimab is FDA approved for treating prostate cancer



CASE 4: PSEUDO-PROGRESSION OF LIVER METS DURING TREATMENT WITH ANTI-PSMA X CD28 + CEMIPLIMAB



01/20/22

02/20/22

04/17/22 PRESENTATION TITLE

05/17/22

05/19/22

Case 4: PSA kinetics during Tx with BiTes & Pluvicto



Neither REGN5678 nor Cemiplimab is FDA approved for treating prostate cancer

SUMMARY

- Ga 68 or Pylarify PSMA PET scan is indicated to stage high risk prostate cancer; to look for early metastasis that maybe amendable for local salve or ablative therapy in the setting of rising PSA after completing initial definitive treatment to cancer in the prostate gland; and to select M1 CRPC patients for Lu177-PSMA-617
- There are no published guidelines on how to use PSMA/PET scan to determine response to treatment
- PSMA expression will diminish when prostate adenocarcinoma is transformed into neuroendocrine or small cell prostate cancer
- Besides radioligands, PSMA targeting bispecific T cell engagers and CAR-T therapy are being tested in early phase clinical trials.

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THANK YOU

Questions?