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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Calais J, Ceci F, Eiber M, et al. ^{18}F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol* 2019; published online July 31. http://dx.doi.org/10.1016/S1470-2045(19)30415-2.

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Supplemental Table 1: Expert readers background and experience

NM : Nuclear medicine physician; RAD: Radiologist.

Reader	Institution	Specialty	Software	PET/CT reading experience (years)	FACBC or PSMA reading experience (years)	Number of FACBC or PSMA reads	Number of FACBC or PSMA publications
T Bach-Gansmo	Oslo, NOR	NM	Syngo Via	13	5	350	9
M Hofman	Melbourne, AU	NM	MIM	14	4	2000	20
T Hope	UCSF, USA	NM + RAD	OsiriX	7	4	1000	8
C Nanni	Bologna, ITA	NM + RAD	GE AW	16	2	150	7
C Rischpler	Essen, GER	NM	Syngo Via	5	5	3000	5
B Savir-Baruch	Chicago, USA	NM	Hermes	10	10	400	14

Supplemental Table 2: PET/CT imaging technical parameters

OSEM: ordered subset expectation maximization; i: iteration; s: subset;

		FACBC		PSMA	
Institution					
	UCLA	38 (76%)		50 (100%)	
	Outside	12 (24%)		-	
Scanner Device					
	Siemens Biograph64 TruePoint	23 (46%)		28 (56%)	
	Siemens Biograph64 mCT	21 (42%)		22 (44%)	
	Siemens Emotion Duo	2 (4%)		-	
	GE Discovery MI	1 (2%)		-	
	GE Discovery RX	1 (2%)		-	
	GE Discovery ST	1 (2%)		-	
	GE Discovery STE	1 (2%)		-	
Contrast					
	Oral	37 (74%)		49 (98%)	
	IV	35 (70%)		48 (96%)	
Reconstruction Algorithm and Parameters					
	3D OSEM (2i, 21s), Gaussian Filter 5.0, pixel 4.07x4.07 mm	19 (38%)		28 (54%)	
	3D OSEM (2i, 24s), Gaussian Filter 5.0, pixel 4.07x4.07 mm	19 (38%)		22 (44%)	
	2D OSEM (2i, 8s), Gaussian Filter 5.0, pixel 5.31x5.31 mm	3 (6%)		-	
	PSF TOF (2i, 21s), pixel 4.07x4.07 mm	2 (4%)		-	
	PSF (3i, 21s), pixel 4.07x4.07 mm	4 (8%)		-	
	GE 3D-IR, pixel 5.47x5.47 mm	2 (4%)		-	
	GE QCFX, pixel 2.73x2.73 mm	1 (2%)		-	
		Median	***IQR***	***Median***	***IQR***
Injected Activity (MBq)		381	359-407	200	192-204
Uptake time (min)		2	1-3	61	57-66
Time-per-bed-position (min)		3.0	2.8-4.0	3.0	2.8-4.0

Supplemental Table 3: Treatment Management after the 2 PET/CT scans (median follow-up of 8 months)

SRT: salvage radiation therapy; SBRT: stereotactic body radiation therapy; LN: lymph node; ADT: androgen deprivation therapy; Abi: abiraterone; Enza: Enzalutamide.

Treatment Management	n (%)
Metastasis Surgery	3 (6%)
Metastasis SBRT	2 (4%)
Prostate Fossa SRT	4 (8%)
Prostate Fossa SRT + Whole-Pelvic LN RT	1 (2%)
Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	1 (2%)
ADT	7 (14%)
ADT + Abi/Enza	2 (4%)
ADT + Prostate Fossa SRT	10 (20%)
ADT + Prostate Fossa SRT + Metastasis SBRT	1 (2%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT	2 (4%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT	3 (6%)
ADT + Prostate Fossa SRT + Whole-Pelvic LN RT + Metastasis SBRT + Abi/Enza	2 (4%)
ADT + Metastasis SBRT	3 (6%)
Surveillance	9 (18%)

Supplemental Table 4: Detailed reads per-region of the 6 expert readers

Bottom row indicate the detection rates.

	PSMA Tr			FACBC Tr			PSMA N			FACBC N			PSMA M1a			FACBC M1a			PSMA M1b			FACBC M1b			PSMA M1c			FACBC M1c			
UCLA #	R1	R2	R3	R4	R5	R6	R1	R2	R3	R4	R5	R6	R1	R2	R3	R4	R5	R6	R1	R2	R3	R4	R5	R6	R1	R2	R3	R4	R5	R6	PSA
UCLA #013	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2
UCLA #014	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2
UCLA #032	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.23
UCLA #026	0	0	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.26
UCLA #043	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.28
UCLA #015	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0.29
UCLA #022	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.29
UCLA #025	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3
UCLA #041	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3
UCLA #044	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0.35
UCLA #018	0	0	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.36
UCLA #007	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.37
UCLA #049	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.38
UCLA #027	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.38
UCLA #003	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0.39
UCLA #019	0	0	0	1	1	0	1	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.39
UCLA #028	0	0	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.39
UCLA #009	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0.4
UCLA #017	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4
UCLA #010	0	0	0	0	0	0	1	1	1	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.43
UCLA #020	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.43
UCLA #050	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0.43
UCLA #004	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.45
UCLA #035	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.46
UCLA #042	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.46
UCLA #012	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.5
UCLA #008	0	0	0	0	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.54
UCLA #030	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.54
UCLA #040	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0.55
UCLA #047	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0.56
UCLA #016	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.6
UCLA #033	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.6
UCLA #039	0	0	1	0	0	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0.6
UCLA #023	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0.62
UCLA #031	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.68
UCLA #021	1	1	1	1	1	0	1	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.72
UCLA #045	0	0	0	0	0	0	1	1	1	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.78
UCLA #002	0	0	0	0	0	0	0	1	0	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0.84
UCLA #011	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.84
UCLA #046	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.84
UCLA #036	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.9
UCLA #001	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.91
UCLA #024	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0.97
UCLA #005	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	1
UCLA #034	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.1
UCLA #037	0	0	1	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.29
UCLA #038	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1.44
UCLA #029	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1.57
UCLA #006	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
UCLA #048	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
	7	6	11	11	7	7	15	16	18	6	4	17	3	2	3	0	3	0	4	1	7	5	0	0	2	1	3	0	2	0	
	14%	12%	22%	22%	14%	14%	30%	32%	36%	12%	8%	34%	6%	4%	6%	0%	6%	0%	8%	2%	14%	10%	0%	0%	4%	2%	6%	0%	4%	0%	

Supplemental Table 5: Detailed reads per-patient of the 6 expert readers

Bottom row indicate the detection rates.

	PSMA positivity			FACBC positivity			
UCLA #	R1	R2	R3	R4	R5	R6	PSA
UCLA #013	0	0	0	0	0	0	0.2
UCLA #014	0	0	0	0	0	0	0.2
UCLA #032	0	0	0	0	0	1	0.23
UCLA #026	1	1	1	1	0	1	0.26
UCLA #043	0	0	1	1	1	1	0.28
UCLA #015	1	1	1	0	0	0	0.29
UCLA #022	1	1	1	1	0	0	0.29
UCLA #025	0	0	0	0	0	0	0.3
UCLA #041	0	0	0	0	0	0	0.3
UCLA #044	1	0	1	1	0	1	0.35
UCLA #018	1	1	1	1	1	0	0.36
UCLA #007	0	0	0	0	0	1	0.37
UCLA #049	1	1	1	0	0	0	0.38
UCLA #027	0	0	1	0	0	1	0.38
UCLA #003	1	1	1	1	0	0	0.39
UCLA #019	1	1	1	1	1	0	0.39
UCLA #028	0	0	1	1	0	1	0.39
UCLA #009	1	1	1	0	1	0	0.4
UCLA #017	0	0	0	0	0	1	0.4
UCLA #010	1	1	1	1	1	1	0.43
UCLA #020	0	1	0	0	0	1	0.43
UCLA #050	1	1	1	1	0	0	0.43
UCLA #004	1	1	1	0	0	1	0.45
UCLA #035	0	0	0	0	0	0	0.46
UCLA #042	0	0	0	1	0	1	0.46
UCLA #012	0	0	0	0	0	0	0.5
UCLA #008	1	1	1	0	1	1	0.54
UCLA #030	0	0	0	0	0	0	0.54
UCLA #040	0	0	1	1	1	0	0.55
UCLA #047	0	0	1	0	0	0	0.56
UCLA #016	0	0	0	0	0	0	0.6
UCLA #033	0	0	0	0	0	0	0.6
UCLA #039	1	1	1	1	0	1	0.6
UCLA #023	1	0	1	1	0	0	0.62
UCLA #031	1	1	1	1	1	1	0.68
UCLA #021	1	1	1	1	1	1	0.72
UCLA #045	1	1	1	1	0	0	0.78
UCLA #002	1	1	1	0	0	1	0.84
UCLA #011	0	0	0	1	1	1	0.84
UCLA #046	1	1	1	1	1	1	0.84
UCLA #036	1	1	1	1	0	0	0.9
UCLA #001	1	1	1	0	0	1	0.91
UCLA #024	1	0	1	0	0	1	0.97
UCLA #005	1	1	1	0	1	0	1
UCLA #034	1	1	1	0	0	0	1.1
UCLA #037	1	1	1	0	0	1	1.29
UCLA #038	1	0	1	1	0	1	1.44
UCLA #029	0	0	1	0	0	0	1.57
UCLA #006	0	0	0	0	0	0	2
UCLA #048	1	0	1	0	0	0	2
	28	24	34	21	12	23	
	56%	48%	68%	42%	24%	46%	

Supplemental Table 6: Detailed majority consensus reads per-region and per-patient of the 50 patients

Bottom row indicate the detection rates.

	PSMA Tr	FACBC Tr	PSMA N	FACBC N	PSMA M1a	FACBC M1a	PSMA M1b	FACBC M1b	PSMA M1c	FACBC M1c	PSMA scan	FACBC scan	PSA
UCLA #013	0	0	0	0	0	0	0	0	0	0	0	0	0.20
UCLA #014	0	0	0	0	0	0	0	0	0	0	0	0	0.20
UCLA #032	0	0	0	0	0	0	0	0	0	0	0	0	0.23
UCLA #026	0	0	1	1	0	0	0	0	0	0	1	1	0.26
UCLA #043	0	0	0	1	0	0	0	0	0	0	0	1	0.28
UCLA #015	0	0	0	0	1	0	0	0	0	0	1	0	0.29
UCLA #022	1	0	0	0	0	0	0	0	0	0	1	0	0.29
UCLA #025	0	0	0	0	0	0	0	0	0	0	0	0	0.30
UCLA #041	0	0	0	0	0	0	0	0	0	0	0	0	0.30
UCLA #044	0	0	0	0	0	0	1	0	0	0	1	0	0.35
UCLA #018	0	1	1	0	0	0	0	0	0	0	1	1	0.36
UCLA #007	0	0	0	0	0	0	0	0	0	0	0	0	0.37
UCLA #049	0	0	1	0	0	0	0	0	0	0	1	0	0.38
UCLA #027	0	0	0	0	0	0	0	0	0	0	0	0	0.38
UCLA #003	1	0	0	0	0	0	0	0	0	0	1	0	0.39
UCLA #019	0	1	1	0	0	0	0	0	0	0	1	1	0.39
UCLA #028	0	1	0	0	0	0	0	0	0	0	0	1	0.39
UCLA #009	0	0	1	0	0	0	0	0	0	0	1	0	0.40
UCLA #017	0	0	0	0	0	0	0	0	0	0	0	0	0.40
UCLA #010	0	0	1	1	0	0	0	0	0	0	1	1	0.43
UCLA #020	0	0	0	0	0	0	0	0	0	0	0	0	0.43
UCLA #050	0	0	0	0	0	0	1	0	0	0	1	0	0.43
UCLA #004	0	0	1	0	0	0	0	0	0	0	1	0	0.45
UCLA #035	0	0	0	0	0	0	0	0	0	0	0	0	0.46
UCLA #042	0	1	0	0	0	0	0	0	0	0	0	1	0.46
UCLA #012	0	0	0	0	0	0	0	0	0	0	0	0	0.50
UCLA #008	0	0	1	0	0	0	0	0	0	0	1	0	0.54
UCLA #030	0	0	0	0	0	0	0	0	0	0	0	0	0.54
UCLA #040	0	0	0	0	0	0	0	0	0	0	0	0	0.55
UCLA #047	0	0	0	0	0	0	0	0	0	0	0	0	0.56
UCLA #016	0	0	0	0	0	0	0	0	0	0	0	0	0.60
UCLA #033	0	0	0	0	0	0	0	0	0	0	0	0	0.60
UCLA #039	0	0	1	1	0	0	0	0	0	0	1	1	0.60
UCLA #023	0	0	0	0	0	0	1	0	0	0	1	0	0.62
UCLA #031	1	1	0	0	0	0	0	0	0	0	1	1	0.68
UCLA #021	1	1	1	0	0	0	0	0	0	0	1	1	0.72
UCLA #045	0	0	1	0	1	0	0	0	0	0	1	0	0.78
UCLA #002	0	0	0	0	1	0	0	0	1	0	1	0	0.84
UCLA #011	0	1	0	0	0	0	0	0	0	0	0	1	0.84
UCLA #046	1	1	0	0	0	0	0	0	0	0	1	1	0.84
UCLA #036	0	0	1	0	0	0	0	0	0	0	1	0	0.90
UCLA #001	0	0	1	0	0	0	0	0	0	0	1	0	0.91
UCLA #024	0	0	0	0	0	0	1	0	0	0	1	0	0.97
UCLA #005	0	0	0	0	0	0	0	0	1	0	1	0	1.00
UCLA #034	1	0	0	0	0	0	0	0	0	0	1	0	1.10
UCLA #037	0	0	1	0	0	0	0	0	0	0	1	0	1.29
UCLA #038	1	1	0	0	0	0	0	0	0	0	1	1	1.44
UCLA #029	0	0	0	0	0	0	0	0	0	0	0	0	1.57
UCLA #006	0	0	0	0	0	0	0	0	0	0	0	0	2.00
UCLA #048	0	0	1	0	0	0	0	0	0	0	1	0	2.00
TOTAL	7	9	15	4	3	0	4	0	2	0	28	13	
	14%	18%	30%	8%	6%	0%	8%	0%	4%	0%	56%	26%	

Supplemental Table 7: Summary of the detection rates per-readers, majority consensus and average

	Expert Reader 1/4	Expert Reader 2/5	Expert Reader 3/6	**Majority Consensus**	Average
T = Local Recurrence					
PSMA	14%	12%	22%	**14%**	16%
FACBC	22%	14%	14%	**18%**	17%
N = Pelvic LN					
PSMA	30%	32%	36%	**30%**	33%
FACBC	12%	8%	34%	**8%**	18%
M1a = Extra-Pelvic LN					
PSMA	6%	4%	6%	**6%**	5%
FACBC	0%	6%	0%	**0%**	2%
M1b = Bone					
PSMA	8%	2%	14%	**8%**	8%
FACBC	10%	0%	0%	**0%**	3%
M1c = Visceral Metastasis					
PSMA	4%	2%	6%	**4%**	4%
FACBC	0%	4%	0%	**0%**	1%
Any M					
PSMA	16%	8%	24%	**16%**	16%
FACBC	10%	10%	0%	**0%**	7%
Patient = Scan					
PSMA	56%	48%	68%	**56%**	57%
FACBC	42%	24%	46%	**26%**	37%

Supplemental Table 8: Paired PET/CT findings of the consensus majority reads (TNM score)

	FACBC	PSMA	n (%)	Cancer Confirmed
Equal false negative (n=18)	T0 N0 M0	T0 N0 M0	18 (36%)	3
Equal positive detection per-patient (n=9)	T+ N0 M0	T+ N0 M0	3 (6%)	3
	T+ N0 M0	T0 N1 M0	3 (6%)	0
	T0 N1 M0	T0 N1 M0	3 (6%)	0
FACBC superior detection per-patient (n=4)	T+ N0 M0	T0 N0 M0	3 (6%)	2
	T0 N1 M0	T0 N0 M0	1 (2%)	0
PSMA superior detection per-patient (n=19)	T0 N0 M0	T+ N0 M0	3 (6%)	0
	T0 N0 M0	T0 N1 M0	8 (16%)	4
	T0 N0 M0	T0 N1 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1a	1 (2%)	0
	T0 N0 M0	T0 N0 M1b	4 (8%)	1
	T0 N0 M0	T0 N0 M1c	1 (2%)	1
	T0 N0 M0	T0 N0 M1a M1c	1 (2%)	1

Supplemental Table 9: Contingency table of the consensus majority reads per-patient

Full Analysis Population (n=50)			**Lesion Validation Population (n=15)**		
	FACBC -	FACBC +		FACBC -	FACBC +
PSMA -	**18**	**4**	PSMA -	**3**	**2**
PSMA +	**19**	**9**	PSMA +	**7**	**3**
	p=0.0026			*p=0.18*	

Supplemental Table 10: Contingency tables of the consensus majority reads per-region for the 50 patients

Tr: Prostate fossa local recurrence

Tr			N			M1a			M1b			M1c			Any M		
	FACBC neg.	FACBC pos.		FACBC neg.	FACBC pos.		FACBC neg.	FACBC pos.		FACBC neg.	FACBC pos.		FACBC neg.	FACBC pos.		FACBC neg.	FACBC pos.
PSMA neg.	38	5	PSMA neg.	34	1	PSMA neg.	47	0	PSMA neg.	46	0	PSMA neg.	48	0	PSMA neg.	42	0
PSMA pos.	3	4	PSMA pos.	12	3	PSMA pos.	3	0	PSMA pos.	4	0	PSMA pos.	2	0	PSMA pos.	8	0
	p=0.73			*p=0.0034*			*p=0.25*			*p=0.13*			*p=0.50*			*p=0.0078*	

Supplemental Table 11: Detection rates per-patient and per-region stratified by PSA category (majority consensus reads)

Region	PET Tracer	< 0.5 (n=26)	0.51-1.00 (n=18)	1.01-2.00 (n=6)
T	*PSMA*	2 (8%)	3 (16%)	2 (33%)
	FACBC	4 (15%)	4 (22%)	1 (17%)
N	*PSMA*	7 (27%)	6 (33%)	2 (33%)
	FACBC	3 (12%)	1 (6%)	0 (0%)
M1a	*PSMA*	1 (4%)	2 (11%)	0 (0%)
	FACBC	0 (0%)	0 (0%)	0 (0%)
M1b	*PSMA*	2 (8%)	2 (11%)	0 (0%)
	FACBC	0 (0%)	0 (0%)	0 (0%)
M1c	*PSMA*	0 (0%)	2 (11%)	0 (0%)
	FACBC	0 (0%)	2 (11%)	0 (0%)
Any M	*PSMA*	3 (12%)	5 (28%)	0 (0%)
	FACBC	0 (0%)	0 (0%)	0 (0%)
PET/CT scan	*PSMA*	12 (46%)	12 (67%)	4 (67%)
	FACBC	7 (27%)	5 (28%)	1 (17%)

Supplemental Table 12: Contingency tables of the majority consensus reads stratified by PSA category (<0.5 / 0.5-1.0 / 1.0-2.0 ng/ml)

Most recent PSA 0.20-0.50 (n=26)

Tr	FACBC		N	FACBC		M1c	FACBC	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	20	4	No	18	1	No	26	0
Yes	2	0	Yes	5	2	Yes	0	0
		p=0.687			p=0.219			p=NA
Distant LN	**FACBC**		**M1b**	**FACBC**		**Positivity**	**FACBC**	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	25	0	No	24	0	No	11	3
Yes	1	0	Yes	2	0	Yes	8	4
		p=1.00			p=0.500			p=0.227

Most recent PSA 0.51-1.00 (n=18)

Tr	FACBC		N	FACBC		M1c	FACBC	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	14	1	No	12	0	No	16	0
Yes	0	3	Yes	5	1	Yes	2	0
		p=1.00			p=0.063			p=0.500
Distant LN	**FACBC**		**M1b**	**FACBC**		**Positivity**	**FACBC**	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	16	0	No	16	0	No	5	1
Yes	2	0	Yes	2	0	Yes	8	4
		p=0.500			p=0.500			p=0.039

Most recent PSA 1.01-2.00 (n=6)

Tr	FACBC		N	FACBC		M1c	FACBC	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	4	0	No	4	0	No	6	0
Yes	1	1	Yes	2	0	Yes	0	0
		p=1.00			p=0.500			p=NA
Distant LN	**FACBC**		**M1b**	**FACBC**		**Positivity**	**FACBC**	
PSMA	No	Yes	PSMA	No	Yes	PSMA	No	Yes
No	6	0	No	6	0	No	2	0
Yes	0	0	Yes	0	0	Yes	3	1
		p=NA			p=NA			p=0.250

Supplemental Table 13: Pairwise Individual Measures of agreement *Kappa 95% Confidence intervals*

PSMA (pairwise Kappa, 95% CI)			FACBC (pairwise Kappa, 95% CI)		
R1 vs R2	**R1 vs R3**	**R2 vs R3**	**R4 vs R5**	**R4 vs R6**	**R5 vs R6**
0.91 (0.63, 1.19)	0.59 (0.32, 0.87)	0.50 (0.23, 0.78)	0.59 (0.32, 0.87)	0.46 (0.18, 0.74)	0.17 (-0.11, 0.45)
0.86 (0.58, 1.14)	0.77 (0.50, 1.05)	0.64 (0.37, 0.92)	0.11 (-0.17, 0.39)	0.15 (-0.12, 0.43)	-0.15 (-0.42, 0.13)
0.79 (0.51, 1.07)	0.65 (0.37, 0.92)	0.37 (0.09, 0.65)	-0.03 (-0.31, 0.25)	NA	-0.03 (-0.31, 0.25)
0.37 (0.09, 0.65)	0.69 (0.42, 0.97)	0.18 (-0.09, 0.46)	-0.05 (-0.33, 0.22)	-0.05 (-0.33, 0.22)	NA
0.66 (0.38, 0.93)	0.79 (0.51, 1.07)	0.48 (0.20, 0.76)	-0.02 (-0.30, 0.26)	NA	-0.02 (-0.30, 0.26)
0.76 (0.48, 1.04)	0.75 (0.47, 1.02)	0.51 (0.23, 0.78)	0.32 (0.04, 0.60)	0.19 (-0.09, 0.47)	0.08 (-0.20, 0.35)

Supplemental Table 14 : Details of the 15 patients with lesion validation

Tr: local recurrence; REI: right external iliac; LEI : left internal iliac; ING: inguinal; RCI: right common iliac; LII: left internal iliac;

Patient #	PSA	FACBC scan	FACBC Final Diagnosis	PSMA scan	PSMA Final Diagnosis	Region Validated	Lesion Validated	Validation Procedure	Management
UCLA #002	0.84	T0 N0 M0	FN	T0 N0 M1a M1c	TP	M1a	R ING LN	Histopathology (biopsy)	SRT Prostate fossa + SRT Pelvis + LN SBRT + ADT
UCLA #004	0.37	T0 N0 M0	FN	T0 N1 M0	TP	N1	LEI LN	Histopathology	Surgery
UCLA #046	0.84	Tr N0 M0	TP	Tr N0 M0	TP	T	Rectal mass	Histopathology	Surgery
UCLA #008	0.54	T0 N0 M0	FN	T0 N1 M0	TP	N1	REI LN	Histopathology	Surgery
UCLA #001	0.83	T0 N0 M0	FN	T0 N1 M0	TP	N1	LII LN	PSA after focal RT no ADT	LN SBRT
UCLA #042	0.46	Tr N0 M0	TP	T0 N0 M0	FN	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #031	0.68	Tr N0 M0	TP	Tr N0 M0	TP	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #025	0.30	T0 N0 M0	FN	T0 N0 M0	FN	T	Prostate Fossa	PSA after focal RT no ADT	SRT Prostate fossa
UCLA #029	1.57	T0 N0 M0	FN	T0 N0 M0	FN	M1b	Pubis	Follow-up imaging (bone scan +CT)	M1b SBRT + ADT
UCLA #030	0.54	T0 N0 M0	FN	T0 N0 M0	FN	M1b	T7	Follow-up imaging (MRI)	Surveillance
UCLA #023	0.62	T0 N0 M0	FN	T0 N0 M1b	TP	M1b	T11	Follow-up imaging (MRI)	Surveillance
UCLA #049	0.38	T0 N0 M0	FN	T0 N1 M0	TP	N1	LO LN	Follow-up imaging (MRI)	SRT Prostate fossa + SRT Pelvis + ADT
UCLA #011	0.84	Tr N0 M0	TP	T0 N0 M0	FN	T	Prostate Fossa	Follow-up imaging (MRI)	SRT Prostate fossa + ADT
UCLA #005	1.00	T0 N0 M0	FN	T0 N0 M1c	TP	M1c	Penis	Follow-up imaging (MRI)	ADT
UCLA #038	1.44	Tr N0 M0	TP	Tr N0 M0	TP	T	Prostate Fossa	Follow-up imaging (Ultrasound)	ADT

Supplemental Table 15: Semi-quantitative analysis and lesion-to-background ratios

L/B: lesion-to-background ratio; Values are mean.

Concordant Lesion	n=	FACBC				PSMA			
		Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle	Lesion SUVmax	L/B Liver	L/B Aorta	L/B muscle
Pelvic LN (N)	3	3.13	0.50	2.18	3.65	5.60	0.94	4.35	13.03
Prostate fossa (T)	4	4.17	0.55	2.71	3.73	10.18	2.24	8.69	34.67
All concordant lesions	**7**	**3.73**	**0.52**	**2.44**	**3.69**	**8.21**	**1.68**	**6.83**	**25.39**

Supplemental Table 16: Summary of multivariable logistic regression mixed effects 9-model with the outcome of positive PET scan.

ADT: androgen deprivation therapy; RT: radiation therapy; RP: radical prostatectomy; NCCN: national comprehensive cancer network.

Model	Covariates	OR (95% CI)	p-value
1	PET Scan tracer (FACBC vs PSMA)	3.88 (1.59-9.45)	0.0036
	on-going ADT	1.49 (0.41-5.41)	0.54
2	PET Scan tracer (FACBC vs PSMA)	3.56 (1.47-8.65)	0.0060
	history of adjuvant ADT	1.18 (0.30-4.15)	0.87
3	PET Scan tracer (FACBC vs PSMA)	3.63 (1.48-8.89)	0.0057
	history of adjuvant RT	0.38 (0.08-1.92	0.24
4	PET Scan tracer (FACBC vs PSMA)	3.65 (1.38-9.65)	0.010
	PSA doubling time > median	0.87 (0.29-2.63)	0.81
5	PET Scan tracer (FACBC vs PSMA)	3.68 (1.39-9.79)	0.010
	PSA Velocity	1.28 (0.68-2.42)	0.437
6	PET Scan tracer (FACBC vs PSMA)	3.58 (1.42-9.04)	0.0081
	NCCN risk group		0.29
	High vs Intermediate	0.41 (0.11-4.49)	0.17
	N1 vs Intermediate	1.40 (0.37-5.25)	0.61
	Very high vs Intermediate	0.45 (0.07-2.75)	0.38
7	PET Scan tracer (FACBC vs PSMA)	3.73 (1.55-8.93)	0.0040
	time RP to PET	1.00 (0.99-1.01)	0.87
8	PET Scan tracer (FACBC vs PSMA)	3.73 (1.56-8.94)	0.0040
	Uptake time > 3 min	1.21 (0.35-4.20)	0.76
9	PET Scan tracer (FACBC vs PSMA)	3.77 (1.57-9.10)	0.0039
	administration of IV CT-contrast	1.68 (0.58-4.86)	0.33

PSMA vs AXUMIN

PET READING SPREADSHEET GUIDELINES

1. Rate the quality of each PET/CT scan as follow : 3 = good quality; 2 = fair quality; 1 = poor quality.
    a. If poor quality (=1), please explain why: CT artefacts, low resolution CT, low tracer activity, high background activity, bladder activity etc …
2. Determine if IV contrast has been administrated: yes =1; no =0.
3. Determine if oral contrast has been administrated: yes =1; no =0.

4. Rate the prostate bed analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
    a. If positive, measure the SUVmax of the prostate bed lesion (if possible with a 3D VOI).
    b. If positive, specify if there is CT correlate: yes =1; no =0.
    c. If positive and with CT correlate, measure the long axis (mm) of the prostate bed lesion

5. Rate the pelvic lymph nodes analysis (below aorto-iliac bifurcation) as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
    a. If positive, specify the number of positive pelvic lymph node(s)
       If positive, specify the localization as follow: RII/LII/RO/LO/REI/LEI/PR/PS/Other (please specify)
       RII= right internal iliac, LII= left internal iliac, RO= right obturator, LO= left obturator, REI= right external iliac, LEI=left external iliac, PR= peri-rectal, PS= pre-sacral.
       If multiple, separate each positive pelvic lymph node by " / "
    b. If positive, measure the SUVmax of the positive pelvic lymph node(s) (if possible with a 3D VOI).
       If multiple, separate each value by " / " (same order than in column AD)
    c. If positive, measure the short axis (mm) of the positive pelvic lymph node(s).
       If multiple, separate each value by " / " (same order than in column AD)

6. Rate the extra-pelvic lymph nodes analysis (above aorto-iliac bifurcation) as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
    a. If positive, specify the number of positive pelvic lymph node(s)
    b. If positive, specify the localization as follow: ABD/SD/ING/Other (please specify)
       ABD= abdominal, SD= supra-diaphragmatic, ING= inguinal.
       If multiple, separate each positive pelvic lymph node by " / "
    c. If positive, measure the SUVmax of the positive extra-pelvic lymph node(s) (if possible with a 3D VOI).
       If multiple, separate each value by " / " (same order than in column AI)
    d. If positive, measure the short axis (mm) of the positive extra-pelvic lymph node(s)
       If multiple, separate each value by " / " (same order than in column AI)

7. Rate the skeletal analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
    a. If positive, specify the number of positive bone lesion
    b. If positive, specify the bone lesion anatomic localization.
       If multiple, separate each positive bone lesion by " / "
    c. If positive, measure the SUVmax of the positive bone lesion(s) (if possible with a 3D VOI).
       If multiple, separate each value by " / " (same order than in column AN)
    d. If positive, specify the CT correlate as follow: NO/SCL/LY/MIX
       If multiple, separate each positive bone lesion by " / " (same order than in column AN).
       NO=None, SCL= sclerotic, LY= Lytic, MIX= Mixed.
    e. If positive and with CT correlate, measure the long axis (mm) of the positive bone lesion(s).
       If multiple, separate each value by " / " (same order than in column AN).

8. Rate the visceral metastasis analysis as negative (=0) or positive (=1). If equivocal findings note these in column AX. You must choose here between 0 and 1.
    a. If positive, specify the number of positive visceral lesion
    b. If positive, specify the visceral lesion anatomic localization.
       If multiple, separate each positive visceral lesion by " / "
    c. If positive, measure the SUVmax of the positive visceral lesion(s) (if possible with a 3D VOI).
       If multiple, separate each value by " / " (same order than in column AS)
    d. If positive, measure the long axis (mm) of the positive visceral lesion(s).
       If multiple, separate each value by " / " (same order than in column AS).

9. Rate the whole body PET/CT scan analysis as negative (=0) or positive (=1).
   If equivocal findings note these in column AX. You must choose here between 0 and 1.

10. Note any equivocal finings or other remarks (AX)

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2.4 PROSPECTIVE SINGLE CENTER TRIAL TO COMPARE 68GA-PSMA-11 AND AXUMIN™ PET/CT (18F-FLUCICLOVINE) FOR RESTAGING PROSTATE CANCER PATIENTS WITH BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY

2.4.1 BACKGROUND AND RATIONALE

While definitive treatment of clinically localized Prostate Cancer (PCa) is highly successful, up to 50% of the patients treated with radical prostatectomy (RP) or external-beam radiotherapy (EBRT) will experience biochemical recurrence during follow-up (1). Various clinical parameters such as serum Prostate Specific Antigen (PSA) levels, PSA doubling time (PSAdt), PSA velocity (PSAvel), pathologic Gleason score, pathologic stage and nodal invasion are used to stratify patients into various risk groups for local vs. systemic recurrence (2). Although these models are characterized by a good accuracy in predicting local versus distant relapse, they cannot predict reliably recurrence sites and extent of metastatic disease. Conventional imaging, including computed tomography (CT), bone scintigraphy (BS) and magnetic resonance (MRI), are insensitive for detecting recurrent PCa at low serum PSA levels.

Thus, patients are generally referred to salvage radiotherapy vs. androgen deprivation therapy (ADT) when a local vs. systemic relapse is suspected. As patients with biochemical recurrence are still potentially curable the ability to precisely localize recurrence site(s) is critically important to stratify patients to best therapeutic approach (i.e., salvage radiation therapy, metastases-directed therapy, medical treatment or combination therapies) (3).

Choline based positron emission tomography (PET) is a useful but suboptimal diagnostic tool for restaging patients with PCa after biochemical recurrence (4,5). Its sensitivity is relatively low especially in patients with low PSA levels at the time of imaging (PSA <2 ng/mL) (5). This is relevant, a salvage therapy can only succeed when serum PSA levels are very low (6).
A new synthetic amino acidic PET tracer, Axumin™ (tradename) (anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid, or ^{18}F-Fluciclovine), has been synthesized and recently tested in PCa patients with suspected tumor recurrence (7, 8). The results obtained by the first prospective studies led to Food and Drug Administration (FDA) approval in 2016 and to Centers of Medicare and Medicaid Services (CMS) reimbursement in 2017 for patients with biochemical recurrence (9). Axumin™ is a substrate of L-amino-acid-transporter-1 (LAT1) and the alanine-serine-cysteine (ASC) transporters (specifically ASCT2) (10, 11). Axumin™ PET/CT has a favorable dosimetry (7) with an effective patient dose of 14.1 µSv/MBq. The average total effective dose is 3.2 mSv, which is significantly lower than that of standard ^{18}F-FDG and slightly higher than that of ^{11}C-Choline (7, 12).

A recent retrospective multicenter trial reported on the efficacy and safety of Axumin™ PET/CT in patients with biochemical recurrence (8). The data of 596 patients at four clinical sites were pooled. The mean PSA at the time of the scan was 5.43 ng/mL and Axumin™ PET/CT was considered positive in 403 of 595 scans, resulting in a positivity rate of 67.7%. The detection rate in the lowest serum PSA quartile (0.79 ng/mL or less) was 41.4%. Histological verification was available in 143 pts (24% of cases) and 119/143 (83.2%) had a positive Axumin™ scan. On a lesion based analysis the sensitivity (90.7 vs. 62.7%) and the positive predictive value (82.4% vs. 62.2%) were lower. As expected, Axumin™ was safe and no significant side effects occurred. In an important study the diagnostic performance of Axumin™ PET/CT was prospectively compared to that of ^{11}C-choline PET/CT in 89 patients with BCR (13). None of the enrolled patients was on Androgen Depravation Therapy (ADT) at the time of the scans. The mean PSA was 6.99 ng/mL. Both tests had a fairly low sensitivity and specificity with Axumin™ PET/CT being marginally more accurate (sensitivity, specificity, PPV, NPV and accuracy for Axumin™: 37 %, 67 %, 97 %, 4 % and 38 %; ^{11}C-Choline: 32 %, 40 %, 90 %, 3 %, 32 %,). It is also noteworthy that in patients with higher serum PSA levels (PSA> 3 ng/mL), Axumin™ PET/CT did not perform as well as expected (sensitivity of 59%). However, it has other advantages over ^{11}C-choline, including ease of production, longer half-life and lower physiologic abdominopelvic background activity.

Highly successful imaging approaches to measure the expression of the prostate specific membrane antigen (PSMA) have been introduced recently. PSMA, the glutamate carboxypeptidase II (GCPII), is a membrane bound metallo-peptidase physiologically expressed in several tissues. Although the function of GCPII in prostate remains unclear, it is well known that this protein is over expressed in in 90-100% of PCa lesions (14, 15). As a consequence, due to its selective overexpression, PSMA is a reliable tissue marker for PCa and is considered an ideal target for tumor specific imaging and therapy (16). The precise localization of the catalytic site of PSMA in extracellular domain allowed for the development of small, highly specific urea-based inhibitors that are internalized inside the cell after ligand binding (17). The agent mostly used in clinical studies (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)]) is labeled with ^{68}Ga (^{68}Ga-PSMA-11). The detection rate of ^{68}Ga-PSMA-11 In 248 patients with BCR after radical prostatectomy was high. ^{68}Ga-PSMA-11 PET/CT detection rates depended on serum PSA levels. They were 97%, 93% and 67% for PSA levels of ≥2, 1 to <2, and 0.2 to <1 ng/mL, respectively (18). ^{68}Ga-PSMA PET is superior to choline PET as shown in several studies (19-21). These investigations also revealed a more favorable tumor to background ratio for ^{68}Ga-PSMA-11 and better sensitivity at very low PSA values (PSA < 2ng/mL). Finally, no adverse events or clinically detectable pharmacological effects occurred after ^{68}Ga-PSMA PET/CT administration (22, 23).
In summary, currently available evidence suggests that Axumin™ PET/CT performs slightly better than choline derivatives. However, emerging data strongly suggests that ^{68}Ga-PSMA targeted imaging identifies sites of biochemical recurrence with a higher sensitivity than Axumin™ (although no direct comparison has been done) especially in the most relevant population, namely those with low PSA levels (18, 24, 25).

2.4.2 STUDY OVERVIEW

Imaging PCa patients with biochemical recurrence is crucial for planning salvage therapy. The aim of this study is the direct comparison of the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT to that of Axumin™ PET/CT in patients with biochemical recurrence at low serum PSA levels (PSA ≤2.0 ng/ml). Axumin™, a substrate of LAT 1 and other amino acid transporters, has received FDA approval for PCa patients with PSA recurrence. ^{68}Ga-PSMA-11 is an investigational PET-agent which is currently under evaluation in several prospective single and multi-center trials. ^{68}Ga-PSMA imaging affects management in around 50% of prostate cancer patients (26). The inter-observer variability is low (27).

Axumin™ PET/CT is marginally more accurate than ^{11}C-choline; However, PSMA targeted imaging appears to identify sites of disease recurrence with a higher sensitivity than choline especially in patients with biochemical recurrence at low PSA levels (PSA <2ng/mL).
Data obtained in this prospective trial will establish evidence for superiority of ^{68}Ga-PSMA-11 compared to the approved imaging probe Axumin™.

2.4.3 STUDY SYNOPSIS

Title	Prospective single center trial to compare ^{68}Ga-PSMA-11 (PSMA-HBED-CC) and Axumin™ (anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid) PET/CT for restaging prostate cancer patients with biochemical recurrence after radical prostatectomy
Patient population	Inclusion criteria: ▪ Histopathologically proven PCa. ▪ Radical Prostatectomy as definitive treatment for PCa ▪ Proven biochemical recurrence as defined by AUA recommendation: PSA greater than or equal to 0.2 ng/mL measured more than 6 weeks after radical prostatectomy. ▪ PSA values ranging from 0.2 ng/mL to 2 ng/mL ▪ No prior salvage therapies (including salvage radiotherapy and/or salvage lymph node dissection); ▪ Axumin™ PET/CT scan already performed or scheduled as best standard of care procedure for suspected disease relapse within 15 days before or after intended ^{68}Ga-PSMA-11 PET/CT. ▪ Karnofsky performance status of ≥50 (or ECOG/WHO equivalent), as reported in Appendix 1. ▪ Age > 18. ▪ Ability to understand a written informed consent document and the willingness to sign it. Exclusion criteria: ▪ Any change in prostate cancer treatment between Axumin™ and ^{68}Ga-PSMA PET/CT scan ▪ Unable to lie flat, still or tolerate a PET scan.
Rationale for Study	^{68}Ga-PSMA-11 PET/CT identifies sites of disease recurrence with a higher accuracy than choline especially in the most relevant population, namely those with low PSA levels (PSA <2ng/mL). Axumin™ PET/CT has slightly better accuracy for the detection of disease recurrence compared to ^{11}C-choline PET/CT. Current literature strongly suggests a superior diagnostic performance of ^{68}Ga-PSMA-11 PET/CT when compared to Axumin™ PET.
Primary Objective	To compare the detection rates of ^{68}Ga-PSMA-11 and Axumin™ PET/CT for the identification of tumor location(s), by patient and region based analysis.

Secondary Objectives	Detection rates on patient based analysis of ^{68}Ga-PSMA-11 and Axumin™ PET/CT stratified by PSA value (0.2 - <0.5; 0.5 - <1.0; 1.0 - <2.0). Sensitivity and positive predictive value (PPV) on a patient based and region based analysis of ^{68}Ga-PSMA-11 PET/CT and Axumin™ PET/CT, confirmed by histopathology/biopsy and/or clinical and conventional imaging follow-up. Inter-observer agreement.
Study Design	Phase 3, single center, open label study.
Number of patients	Total population of patients will be 50 patients.
Duration of Therapy	The study will involve one investigational imaging study and one investigational radiopharmaceutical. Patients eligible have already undergone one (1) Axumin™ PET/CT scan or will undergo one (1) Axumin™ PET/CT, already scheduled as best standard of care procedure, within 15 days before or after the investigational scan.
Duration of Follow up	The length of follow-up will be 12 months for each patient. All relevant clinical and pathological data required to validate PET findings will be collected. These include all clinical and imaging data, subsequent treatments, pathology findings, etc.
Duration of study	The study will reach completion within 26 months from the time the study opens to accrual.
Study Drug	Gallium-68 labeled PSMA-11 (PSMA-HBED-CC)

2.4.4 OBJECTIVES OF THE STUDY

2.4.4.1 Primary end-point

- To compare the detection rates of ^{68}Ga-PSMA-11 PET/CT and Axumin™ PET/CT for the identification of tumor location(s), by patient and region based analysis.

2.4.4.2 Secondary end-points

- 2.1 Detection rate on a per-patient basis of ^{68}Ga-PSMA-11 PET/CT and Axumin™ PET/CT, stratified by PSA value (0.2 - <0.5; 0.5 - <1.0; 1.0 - <2.0).

- 2.2 Sensitivity and positive predictive value (PPV) on a per-patient basis, of ^{68}Ga-PSMA-11 PET/CT and Axumin™ PET/CT for the detection of tumor location(s), confirmed by histopathology/biopsy and/or clinical and conventional imaging follow-up.

- 2.3 Agreement among the readers, separate for ^{68}Ga-PSMA-11 PET/CT versus Axumin™ PET/CT

2.4.5 STUDY DESIGN

2.4.5.1 Study Description

This is a prospective, phase 3, single center, open-label study in PCa patients with biochemical recurrence after radical prostatectomy. Eligible participants (i.e., those with biochemical recurrence and an Axumin™ scan performed within 15 days) will undergo baseline assessments at enrollment.

Patients will be enrolled by faculty of the Nuclear Medicine Clinic of the David Geffen School of Medicine at the University of California, Los Angeles (UCLA).

^{68}Ga-PSMA-11 PET/CT will be performed as investigational diagnostic procedure in PCa patients with biochemical recurrence. All patients eligible in the study must have already undergone or be scheduled for a clinically indicated Axumin™ PET/CT performed as standard of care within 15 days before or after the ^{68}Ga-PSMA-11 PET/CT scan. In case Axumin™ PET has not been performed in the Nuclear Medicine at UCLA, the DICOM images of the Axumin™ scan will be collected.

This is an outpatient imaging study and participants will receive a one-time administration of the investigational radiopharmaceutical ^{68}Ga-PSMA-11 for PET/CT imaging. ^{68}Ga-PSMA-11 PET/CT will be performed within 15 days before or after Axumin™ PET/CT. The patient follow-up will last for 12 months.

2.4.5.2 Number of Subjects

The study requires the enrolment of 50 patients with PCa with proven biochemical recurrence after radical prostatectomy as definitive therapy.

2.4.5.3 Eligibility Criteria

Patients must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. Written informed consent must be obtained prior to enrollment.

Inclusion Criteria

- Histopathologically proven PCa.
- Radical Prostatectomy as definitive treatment for PCa
- Proven biochemical recurrence as defined by AUA recommendation: PSA greater than or equal to 0.2 ng/mL measured more than 6 weeks after radical prostatectomy.
- PSA values ranging from 0.2 ng/mL to 2 ng/mL
- No prior salvage therapies (including salvage radiotherapy and/or salvage lymph node dissection);
- Axumin™ PET/CT scan already performed or scheduled as best standard of care procedure for suspected disease relapse within 15 days before or after intended ^{68}Ga-PSMA-11 PET/CT
- Karnofsky performance status of ≥50 (or ECOG/WHO equivalent), as reported in Appendix 1.
- Age > 18.
- Ability to understand a written informed consent document and the willingness to sign it.

Exclusion Criteria

- Any change in prostate cancer treatment between Axumin™ and ^{68}Ga-PSMA PET/CT scan
- Unable to lie flat, still or tolerate a PET scan.

2.4.5.4 Duration of Enrollment and Follow UP

Anticipated enrollment duration: we anticipate an enrollment duration of 12 months to recruit 50 patients.

The follow-up will be a maximum of 12 months for each patient. This duration is required to obtain clinical data to verify imaging findings.

2.4.5.5 Study Timeline and GANTT Chart

1. Patients' enrollment. Duration: 12 months
2. Clinical and diagnostic follow-up. Duration: 24 months
3. Data collection. Duration: 24 months
4. Data analysis. Duration: 2 months
5. Data diffusion and publication. Duration: 2 months

The project timetable is exposed by a Gantt chart, as displayed in Appendix 2.

2.4.5.6 Study Completion

The study will reach study completion 26 months from the time the study opens to accrual.

2.4.6 STUDY DRUG

^{68}Ga-PSMA-11 (or PSMA-HBED-CC) is a radiopharmaceutical that will be produced and supplied by UCLA Ahmanson Biomedical Cyclotron and Radiochemistry Facility

2.4.7 CLINICAL PLAN

2.4.7.1 Dosage and Administration

The imaging agent (^{68}Ga-PSMA-11) will be administered on an outpatient basis. The radiopharmaceuticals will be administered a single time intravenously prior to the PET imaging. The injected dose for ^{68}Ga-PSMA-11 will be 3-5 mCi.

2.4.7.2 PET Imaging

a) Preparation and injection: the intravenously injected dose will be 3-5 mCi of ^{68}Ga-PSMA-11 PET. A dose of 20 mg of furosemide (Lasix) will be injected i.v. shortly before the administration of the radiotracer to empty the urinary bladder. Oral hydration is recommended on the day of the scan. Voiding is recommended immediately before start of the scan. Furosemide should not be administered in patients with medical contraindications to Furosemide administration including allergies and adverse reactions including sulfa allergies. PET imaging will begin 60-90 minutes after injection. Scan time is 3 minutes per bed position.
b) Patient preparation: no fasting is required.
c) PET protocol: Scan coverage will extend from top of the skull to toes, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. Bed position scan time will be 3 minutes per bed position. In certain circumstances, coverage may be extended to the toes. Contrast may be administered if requested by the referring clinician.
d) Patient monitoring: Vital signs will be assessed immediately before and after injection of ^{68}Ga-PSMA-11 (heart rate and supine blood pressure). Additionally, patient's vitals will be checked at the completion of the imaging study prior to leaving the imaging center.
e) Patient follow-up: Patients will be contacted one to three days after ^{68}Ga-PSMA-11 PET to assess for the development of delayed adverse events. Patients will be seen in the clinic if there are any concerning study related adverse events requiring further evaluation.

2.4.7.3 Safety Monitoring

Each patient receiving ^{68}Ga-PSMA-11 will be evaluated for safety. The safety parameters include blood pressure and heart rate before and after the ^{68}Ga-PSMA11 PET/CT and spontaneous reports of adverse events reported to the investigator by patients.

2.4.8 STUDY PROCEDURES AND OBSERVATIONS

2.4.8.1 Schedule Procedures and Observations

Screening assessments must be performed within 30 days prior to the first dose of investigational products (^{68}Ga-PSMA-11). Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation. The schedule of study procedures and assessments is displayed in Appendix 3.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

2.4.8.1.1 Patient Screening

Information needed for patient enrollment must be obtained:

- Laboratory values: all patients must have a recent PSA (within 30 days prior to study enrollment) consistent with BCR.
- Pathology: all patients must have documentation of histopathology/biopsy of the prostate with proven PCa.
- Axumin™ PET: in case Axumin™ PET has not been performed in the Nuclear Medicine at UCLA, the DICOM images of the Axumin™ scan must be collected (within 15 days before or after the ^{68}Ga-PSMA-11 PET/CT scan).
- Performance status: all patients must have their Karnofsky performance status (or ECOG/WHO equivalent) evaluated (Appendix 1).

2.4.8.1.2 Patient Visit

PET Imaging day: Patient enrolled in this study will be administered of the investigational drug and undergo PET scan. Safety monitoring will be performed during the PET imaging. Any adverse event will be documented and evaluated.

2.4.8.1.3 Patient Follow-up

Patients will be followed for 12 months after ^{68}Ga-PSMA-11 PET/CT scan. During follow-up, all clinical and pathological data useful to validate ^{68}Ga-PSMA-11 PET/CT findings (true versus false) will be collected.

2.4.9 EVALUATION OF SIDE EFFECTS

2.4.9.1 Evaluation of Adverse Events

Analyses will be performed for all patients receiving ^{68}Ga-PSMA-11 and Axumin™. The study will use the CTCAE v4.0 for reporting of adverse events.

2.4.9.2 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick if given by intravenous injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body. This research study involves exposure to radiation from one ^{68}Ga-PSMA-11 PET/CT. The effective dose from one typical 3.8 mCi administration of ^{68}Ga-PSMA-11 is 3.54 mSv. The effective dose from one CT attenuation scan is 4 mSv. Therefore, the effective dose from one ^{68}Ga-PSMA-11 PET/CT is 7.54 mSv, approximately equal to 15% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. A detailed definition of different pattern of adverse events is reported in Appendix 4.

2.4.9.3 Adverse Events Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (i.e., each dose will be double-checked for dosimetry and quality by a researcher and technologist). The study Principal Investigator (PI) or his designee will report unanticipated AEs to the UCLA IRB within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death). If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible. Adverse events will be reported to the FDA.

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	**Attribution**	**Description**
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as none, mild, moderate or severe according to the following grades and definitions as exposed in Appendix 5.

2.4.10 STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

2.4.10.1 Study Endpoints

The primary end-point is the direct comparison of ^{68}Ga-PSMA-11 and Axumin™ detection rates for the identification of tumor location(s), assessed by patient and region based analysis.

2.4.10.2 Randomization

No randomization will be performed. Readers will be blinded for all clinical data

2.4.10.3 Determination of Sample Size and Accrual Rate Estimation

The primary endpoint is to evaluate the detection rate on a (1) per-patient and (2) per-region-basis (prostate bed, pelvic lymph-nodes, extra-pelvic lymph-nodes, bone metastases, other soft tissue; Table 1) of ^{68}Ga-PSMA-11 PET and Axumin™ for the detection of tumor location(s).

Table 1

Region	Description
1	Prostate Bed
2	Pelvic lymph-nodes
3	Extra-pelvic lymph-nodes (retroperitoneal, abdominal, mediastinal, other)
4	Bone metastases
5	Other soft tissue: organ metastases (non-bone)

It is anticipated that for Axumin™ PET/CT the detection rate on a per-patient basis ranges from 21 to 59% (estimated mean 47%) in patients with biochemical recurrence and PSA ≤2 ng/mL (28-30). It is anticipated that for ^{68}Ga-PSMA-11 PET/CT the detection rate on a per-patient basis ranges from 61 to 82% (estimated mean 69%) in patients with biochemical recurrence and PSA ≤2 ng/mL (31-33). A 27% probability is estimated for prostate cancer localization by ^{68}Ga-PSMA-11 PET/CT in patients that were negative on Axumin™ PET/CT based on a case series and the authors clinical experience. Based on these estimates a contingency table for Axumin™ versus ^{68}Ga-PSMA-11 PET/CT detection rate on a patient basis is outlined in Table 2.

Table 2

		^{68}Ga-PSMA-11	
		+	-
Axumin™	+	42%	5%
	-	27%	26%

We estimate that 50 patients with PCa will be enrolled during the 12 months of enrollment as required for this study.

The one-sided McNemar exact conditional test (34) will be used to test the null hypothesis $H_0: p_1 - p_2 = 0$ that there is no difference in the detection rate between ^{68}Ga-PSMA-11 PET/CT

and Axumin™ PET/CT versus the alternative hypothesis $H_a: p_1 - p_2 = 0.22$ that the detection rate for PSMA-11 PET/CT is higher than that for Axumin™ PET/CT. A sample size of 50 patients provides at least 86% power to detect the expected difference (22%) in rates of positivity between ^{68}Ga-PSMA-11 and Axumin™ , assuming a one-sided alpha of 0.05.

2.4.10.4 Analysis Plans

2.4.10.4.1 Analysis Population

All enrolled patients will be analyzed for the evaluation of the detection rate, as reported in primary endpoint and the secondary endpoint 2.1.

In the analysis of sensitivity and PPV on a per-patient basis (secondary endpoint 2.2) will be evaluated only patients in whom histopathology/biopsy and/or clinical and conventional imaging follow-up data will be available.

2.4.10.4.2 Image interpretation for ^{68}Ga-PSMA-11 PET and Axumin™ PET

For the local reads, ^{68}Ga-PSMA-11 PET images and Axumin™ PET images will be interpreted independently, by two board certified nuclear medicine physicians (or board-certified radiologists experienced in reading PET) at the time of the imaging study, respectively.

For central reads, anonymized images will be sent to three external board certified nuclear medicine physicians (or board-certified radiologists experienced in reading PET). ^{68}Ga-PSMA-11 PET/CT and Axumin™ PET/CT will be read by separate and independent readers in a randomized order. Central readers will be blind about the local PET/CT results.

The majority interpretations of the central readers will be used for the final evaluation and reported as part of the primary or secondary endpoints.

2.4.10.4.3 Reader Positivity and Negativity Definition

Regions will be defined as prostate bed, pelvic lymph-nodes, extra-pelvic lymph-nodes, bone lesions and other soft tissue lesions as reported in Table 1.

Criteria for visual interpretation for ^{68}Ga-PSMA-11 PET and Axumin™ PET: regions of suspected disease will be graded on a two-point scale by each blinded reader (0=Negative or 1= Positive). A region will be judged as positive if at least one lesion in this region is visually positive.

1) Prostate bed lesions will be considered positive if the uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.
2) Lymph nodes will be considered positive if the uptake is focal and greater than blood pool (adjacent or mediastinal blood pool).
    - Lymph nodes will be classified further by region: pelvic, retroperitoneal, abdominal, thoracic, and other. Additionally, pelvic lymph nodes will be subclassified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups).

3) Bone lesions will be considered positive if the uptake is focal and greater than physiologic bone marrow.
   - Bone lesions will be classified by further by region: spine, ribs, pelvis, extremities, skull, sternum, and clavicle.
4) Visceral lesions will be considered positive if the uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.
   - Visceral lesions will be classified further by major organ: lung, liver, pancreas, spleen, kidneys, stomach, intestine, mesentery, and other tissue.

2.4.10.4.4 Analysis of Primary Endpoint

The detection rate, on a per-patient and per-region analysis, of ^{68}Ga-PSMA-11 PET and Axumin™ PET for detection of tumor location(s) will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

Detection rate in the per-patient analysis is defined as number of patients with PET positive disease, independent of pathology or imaging/clinical follow-up.

Detection rate in the per-region analysis is defined as number of regions (prostate bed, pelvic lymph-nodes, extra-pelvic lymph-nodes, bone metastases, other soft tissue, as exposed in Table 1) resulted PET positive, independent of pathology or imaging/clinical follow-up.

2.4.10.4.5 Analysis of Secondary Endpoints

1. Secondary endpoint 2.1: detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET and Axumin™ PET will be stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5.0) and will be summarized in tabular format and compared between PSA using chi-square analysis. Detection rate is defined as number of patients with PET positive disease, independent of pathology, imaging or clinical follow-up.

2. Secondary endpoint 2.2: sensitivity and PPV by-patient and region-based analysis of ^{68}Ga-PSMA-11 PET and Axumin™ PET for detection of tumor location(s). The sensitivity and PPV will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

Only patients having histopathology/biopsy and/or clinical and conventional imaging follow-up will be analyzed for this secondary end-point.

Since pathology is generally considered superior to imaging and clinical follow-up the validation of ^{68}Ga-PSMA-11 PET and Axumin™ PET should be preferably performed by histopathology or biopsy, when clinically feasible. Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol. Histopathological procedures and biopsies performed within two months and during the entire the follow-up period will be considered

acceptable. In case of positive histopathology/biopsy, the confirmed sites of metastatic or tumor involvement (true positive) will be discussed with the responsible physician/surgeon. In case of negative histopathology/biopsy, the PET finding will be considered false positive, unless dedicated CT, MRI or a repeat PET/CT reveal the persistence of the suspected lesion(s).

When the histopathological confirmation of PET findings will be not clinically feasible, ^{68}Ga-PSMA-11 PET and Axumin™ PET results will be confirmed by clinical and conventional imaging follow-up as reported in details in Appendix 6.

3. Secondary endpoint 2.3: Agreement will be calculated separately for 68Ga-PSMA-11 PET/CT versus Axumin™ PET/CT. For binary data, agreement among central readers will be evaluated using Fleiss´ κ. For non-binary data with more than ten observations, agreement among central readers will be evaluated by interclass correlation coefficient (ICC). Ninety-five percent confidence intervals (CIs) will be reported for κ and ICC values. Interpretation of κ and ICC will be based on a classification provided by Landis and Koch: 0.0, poor; 0.0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost-perfect reproducibility.

2.4.11 REGULATORY CONSIDERATIONS

2.4.11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCLA IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Principal Investigator will disseminate the protocol amendment information to all participating investigators.

2.4.11.2 Data Management Plan

The CRFs will be stored in a locked office in the Nuclear Medicine Clinic.

During the clinical investigation, the Principal Investigator will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome.

2.4.11.3 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient’s medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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List of Abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
BS	Bone scintigraphy
CHR	Committee on Human Research
CRC	Clinical Research Coordinator
CRF	Case report form
CT	Computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
FACBC	Anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid
FDA	Food and Drug Administration
^{18}F	Fluorine 18
^{68}Ga	Gallium 68
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
LND	Lymph node dissection
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
PCa	Prostate Cancer
PET	Positron Emission Tomography
PK	Pharmacokinetics
PRC	Protocol Review Committee (UCSF)
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
RP	Radical prostatectomy
SD	Standard deviation

Appendix

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2: Project timetable (Gantt Chart)

List of activities	M 0	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16	M 17	M 18	M 19	M 20	M 21	M 22	M 23	M 24	M 25	M 26
A1 NM+U																											
A2 NM+U																											
A3 NM																											
A4 NM+U																											
A5 NM+U																											
A6 NM+U																											
A7 NM+U																											

Legend: M= Month; A= Activity. U= Department of Urology; NM= Department of Nuclear Medicine

List of activities:

A 1 Case report form (CRF) creation; authorizations; physicians' meetings.
A 2 Patients enrolment. Duration: 12 months
A 3. PET/CT scans. Duration: 12 months
A 4 Clinical evaluation, patients' management and clinical follow-up Duration: 24 months
A 5 Data collection. Duration: 24 months
A 6 Data analysis. Duration: 2 months
A 7 Data diffusion and publication. Duration: 2 months

Appendix 3: Schedule of Study Procedures and Assessments

	Schedule of Study Procedures and Assessments				
Period/ Procedure	**Screening**	**Imaging day 1**	**1-3 days post imaging**	**1-14 days post imaging**	**Follow-up surveys**
Study Day/Visit Day	-30 to 1 (days)	1 (days)	2 to 4 (days)	2 to 15 (days)	2 to 365 (days)
Informed consent	X				
Laboratory values, history from medical record	X				
Axumin™ PET/CT DICOM images and report (if performed prior to investigational scan)	X				
Axumin™ PET/CT DICOM images and report (if performed after investigational scan)				X	
Performance status	X				
	Imaging Procedure: ^{68}Ga-PSMA-11				
^{68}Ga-PSMA-11		X			
PET/CT		X			
	Follow-up				
Adverse event reporting			X		
Post-survey					X

Appendix 4: Adverse Event Description

Pattern of adverse event	Description
Suspected	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.
Unexpected	Any adverse event not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Adverse events that would be anticipated to occur as part of the disease process are considered unexpected for the purposes of reporting because they would not be listed in the investigator brochure
Serious	Any adverse event that results in any of the following outcomes: ▪ Death ▪ Life-threatening adverse event ▪ Inpatient hospitalization or prolongation of existing hospitalization ▪ A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function ▪ Congenital anomaly/birth defect Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Life-threatening	Any adverse event that places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Appendix 5: Categories of Adverse Events

Grade	Description
0	No AE (or within normal limits)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated

Appendix 6: 68Ga-PSMA-11 PET validation based on follow-up imaging

^{68}Ga-PSMA-11 PET validation based on follow-up imaging	
Prostate bed	a. True positive: - If on follow-up imaging within 12 months, lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter. - If patients with prostate bed lesions only show a decrease of PSA by ≥50% after targeted treatment (i.e. external beam radiation)
	b. False positive: - If on follow-up imaging within 12 months, sites of initial ^{68}Ga-PSMA-11 positive lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.
Lymph nodes	a. True positive: - If on follow-up imaging within 12 months, lymph nodes seen on CT or MRI decrease by more than 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size). - If patients with solitary lymph node regions show a decrease of PSA by ≥50% after targeted treatment (i.e. external beam radiation)
	b. False positive: - If on follow-up imaging within 12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.
Bone lesions	a. True positive: - If there was a corresponding suspicious sclerosis / sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-11 PET in the same location as the PSMA uptake. - If there is focal uptake seen on the baseline bone scan performed within one month of ^{68}Ga-PSMA-11 PET. - If there is a lesion noted on the initial MRI performed within one month of ^{68}Ga-PSMA-11 PET. - If within 12 months follow-up CT demonstrates development of sclerosis. - If within 12 months follow-up MRI demonstrates a new bone lesion. - If within 12 months follow-up bone scan demonstrates new focal uptake.
Visceral lesions	a. True positive: - If on follow-up imaging within 12 months, visceral lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter. - If patients with solitary visceral metastasis show a decrease of PSA by ≥50% after targeted treatment (i.e. external beam radiation)
	b. False positive: - If on follow-up imaging within 12 months, sites of initial ^{68}Ga-PSMA-11 positive lesions seen on CT or MRI decrease by more than 30% without systemic therapy or focal therapy at this site.

Lesions not meeting above criteria for false positive or true positive findings will be indeterminate.