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A prospective, phase 2/3 multi-center study of ^{18}F-DCFPyL PET/CT imaging in patients with prostate cancer- examination of diagnostic accuracy (OSPREY)

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Disclosures

- This study was funded by Progenics Pharmaceuticals, Inc., which has a proprietary commercial interest in ^{18}F-DCFPyL (PyL™)

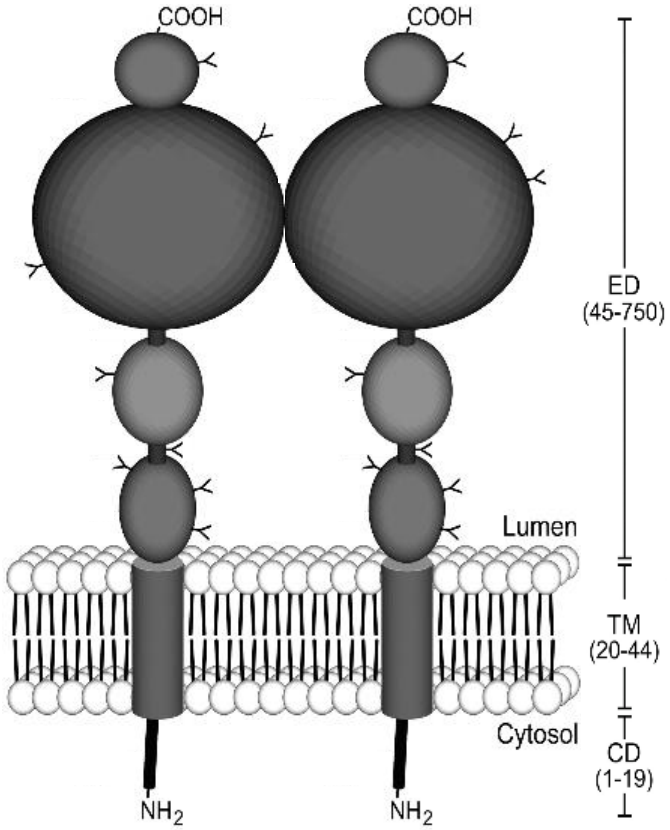
Background

- Current imaging modalities are inadequate to detect prostate cancer (PCa) metastases
- CT and MRI have poor predictive value for regional disease (N1) at preoperative staging
- No approved PET imaging agents for preoperative staging
- PSMA-targeted PET imaging may be applied to staging of patients at risk of harboring occult metastatic PCa

Siegel *et al.* JCO 2019; Hövels *et al.* Clin Radiol 2008; Mohler *et al*. NCCN Prostate Cancer v.2.2018

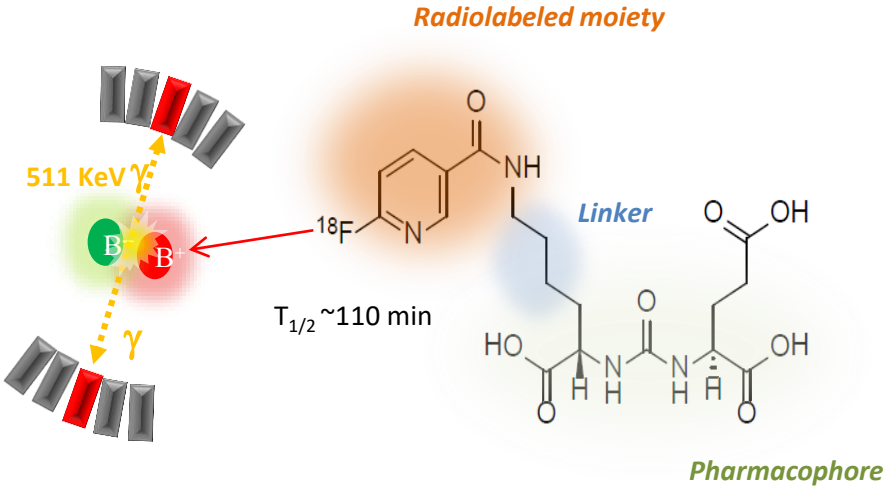
Prostate-specific membrane antigen (PSMA)

- Dimerized type II transmembrane glycoprotein
- Catalyzes the hydrolysis of N-acetylaspartylglutamate (NAAG) to glutamate
- Overexpressed by prostate cancer epithelial cells
- Found in the neovasculature of a number of other solid malignancies including renal cell carcinoma



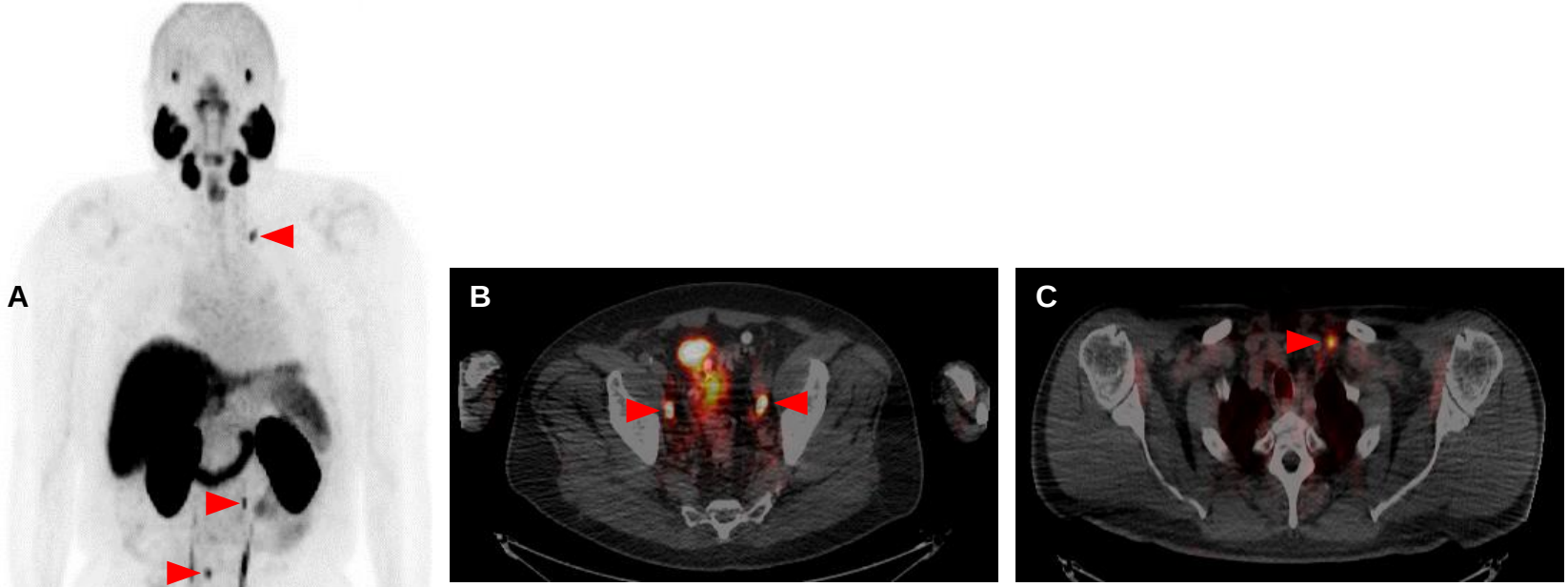
^{18}F-DCFPyL

- ^{18}F-labeled small molecule inhibitor of PSMA
- 9 mCi (333 MBq), which is lesser than with ^{18}F-FDG
- All organ exposures are < 50 mGy



Chen *et* al; Clin Cancer Res. 2011; Szabo *et al*. Mol Imag Biol 2015

^{18}F-DCFPyL PET/CT for Preoperative Staging



Gorin et al., *J Urol*. 2018; 199: 126

JHU phase 1/2 results: Preoperative staging

Table 2. *Diagnostic performance of ^{18}F-DCFPyL PET/CT for detecting pelvic lymph node metastases*

Analysis Level	% (95% CI)
Pt:	
Sensitivity	71.4 (29.0—96.3)
Specificity	88.9 (65.3—98.6)
Pos predictive value	71.4 (38.4—90.9)
Neg predictive value	88.9 (71.0—96.3)
Packet:	
Sensitivity	66.7 (29.9—92.5)
Specificity	92.7 (80.1—98.5)
Pos predictive value	66.7 (38.0—86.7)
Neg predictive value	92.7 (83.4—97.0)

Gorin MA et al. *J Urol.* 2018

OSPREY Study Design and Objectives (NCT02981368)

Total subjects: N=**385**

Cohort A (N=268) Subjects with At least high risk prostate cancer *planned for Radical Prostatectomy* **(Prostate Gland)** *with an Extended Pelvic Lymph Node Dissection* **(Pelvic Lymph Nodes)**

Primary Endpoints: ***Sensitivity and specificity*** within the **pelvic lymph nodes** relative to histopathology

Key Secondary Endpoints:
- **PPV and NPV** within **prostate gland** and **pelvic lymph nodes**
- **Detection rates** between PyL and conventional imaging

Cohort B (N=117) *Radiologic evidence of metastasis or recurrence for biopsy* **(Metastatic Lesions)**

Key Secondary Endpoints:
- **Sensitivity** within **metastatic lesions** relative to histopathology
- **PPV** within **metastatic lesions**
- **Detection rates** between PyL and conventional imaging

Exploratory Endpoints:
- Changes to clinical management
- **PPV** of PyL imaging in subjects that undergo a change of management
- SUV correlations to PSA, testosterone and Gleason Score

- **3 independent, central readers**
- **Histopathology truth standard**

OSPREY: Enrollment and Disposition

Parameter	Cohort A N (%)	Cohort B N (%)	Overall N (%)
Consented Set			462
Screen Failure			77 (16.7)
Safety Set	268	117	385
Evaluable Set	252 (94.0)	93 (79.5)	345 (89.6)
Per-Protocol Set	246 (91.8)	92 (78.6)	338 (87.8)
Change in Planned Protocol Procedure set	12 (4.5)	5 (4.3)	17 (4.4)
PK Blood Set	10 (3.7)	0	10 (2.6)
PK Urine Set	10 (3.7)	0	10 (2.6)

- A total of 385 subjects were dosed; 70% in cohort A and 30% in cohort B
- No subjects discontinued due to adverse event

OSPREY: Select Baseline Characteristics

Characteristic	Cohort A (n=252)	Cohort B (n=93)
Age (years) Median (range)	64.5 (46 – 84)	68 (45 – 86)
PSA[1] (ng/mL) Median (range)	9.3 (1.2 – 86.2)	11.3 (0.03 – 596.9)
T Stage, n (%) T2 (2a,2b,2c) T3 (3a, 3b) T4	 92 (36.5) 67 (26.6) 1 (0.4)	 24 (25.8) 32 (34.4) 8 (8.6)
N Stage, n (%) N0/NX N1	 244 (96.8) 8 (3.2)[2]	 66 (71.0) 23 (24.7)
Gleason Sum, n (%)[2] 6-7 8 9 10	 49 (19.4) 115 (45.6) 85 (33.7) 3 (1.2)	 30 (32.3) 26 (28.0) 33 (35.5) 0

Key inclusion criteria:
- *Cohort A: at least high risk PCa as defined by NCCN: ≥cT3a or PSA>20 or GS ≥8*
- *Cohort B: conventional imaging finding of recurrent/metastatic PCa*

1. Baseline PSA was measured in 251 evaluable cohort A subjects and all 93 evaluable cohort B subjects
2. Of the 8 N1 cohort A subjects, six subjects reflect cN1 by conventional imaging before ^{18}F-DCFPyL PET/CT and surgery, and two subjects reflect pN stage (data was recorded after positive lymph node pathology). Of the 6 cN1, 33.3% (2/6) were found to be N0 by both surgical pathology and ^{18}F-DCFPyL PET/CT

OSPREY: Summary of Adverse Events (Safety)

	Statistic	Cohort A (N=268)	Cohort B (N=117)	Overall (N=385)
At Least One Treatment-Emergent AE (TEAE)	n (%)	39 (14.6)	12 (10.3)	51 (13.2)
At Least One Drug-Related TEAE	n (%)	25 (9.3)	2 (1.7)	27 (7.0)
At Least One >=Grade 3 TEAE	n (%)	1 (0.4)	4 (3.4)	5 (1.3)
At Least One Drug-Related TEAE with Grade>=3	n (%)	1 (0.4)	0	1 (0.3)
At Least One TEAE Leading to Subject Discontinuation	n (%)	0	0	0
At Least One TEAE Leading to Drug Interrupted	n (%)	0	0	0
At Least One TEAE Leading to Dose Reduced	n (%)	0	0	0
At Least One TEAE Leading to Drug Withdrawn	n (%)	0	0	0
At Least One Serious TEAE	n (%)	1 (0.4)	6 (5.1)	7 (1.8)
Non-Fatal	n (%)	1 (0.4)	6 (5.1)	7 (1.8)
Fatal	n (%)	0	0	0

- **A total of 27 (7%) subjects experienced at least one drug-related adverse event as determined by the investigator**
- **There were no serious drug-related adverse events**

OSPREY: Drug-related adverse events

System Organ Class Preferred Term	Cohort A (N=268) Subjects n (%)	 Events n	Cohort B (N=117) Subjects n (%)	 Events n	Overall (N=385) Subjects n (%)	 Events n
Any Drug-Related TEAE	25 (9.3)	38	2 (1.7)	2	27 (7.0)	40
Nervous system disorders	15 (5.6)	22	1 (0.9)	1	16 (4.2)	23
Dysgeusia	7 (2.6)	7	1 (0.9)	1	8 (2.1)	8
Headache	8 (3.0)	10	0	0	8 (2.1)	10
Dizziness	1 (0.4)	1	0	0	1 (0.3)	1
Hyperaesthesia	1 (0.4)	1	0	0	1 (0.3)	1
Migraine	1 (0.4)	1	0	0	1 (0.3)	1
Visual field defect	1 (0.4)	2	0	0	1 (0.3)	2
General disorders and administration site conditions	7 (2.6)	7	0	0	7 (1.8)	7
Fatigue	3 (1.1)	3	0	0	3 (0.8)	3
Application site rash	1 (0.4)	1	0	0	1 (0.3)	1
Chest discomfort	1 (0.4)	1	0	0	1 (0.3)	1
Feeling abnormal	1 (0.4)	1	0	0	1 (0.3)	1
Injection site pain	1 (0.4)	1	0	0	1 (0.3)	1

- **The most frequent drug-related AEs were dysgeusia (2.1%) and headache (2.1%)**

^{18}F-DCFPyL PET in metastatic PCa (cohort B)

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Biopsied tissue category	Reader	Sensitivity (95% CI)	PPV (95% CI)
Overall (all metastatic lesions)	1	98.6% (0.916, 1.0)	81.2% (0.729, 0.89)
	2	95.8% (0.88, 0.99)	81.9% (0.737, 0.90)
	3	92.9% (0.84, 0.97)	87.8% (0.80, 0.95)
Bone	1	96.8% (0.82, 1.0)	78.9% (0.66, 0.919)
	2	96.9% (0.829, 1.0)	81.6% (0.69, 0.939)
	3	90.3% (0.74, 0.97)	82.3% (0.695, 0.95)
Lymph Nodes	1	100% (0.86, 1.0)	81% (0.68, 0.937)
	2	93.3% (0.776, 0.99)	80% (0.668, 0.93)
	3	96.7% (0.819, 1.0)	90.6% (0.75, 0.975)
Visceral/soft tissues	1	100% (0.655, 1.0)	90% (0.57, 1.0)
	2	100% (0.655, 1.0)	90% (0.57, 1.0)
	3	88.9% (0.54, 1.0)	100% (0.62, 1.0)

^{18}F-DCFPyL PET/CT in high-risk patients (cohort A), subject level

Cohort A Tissue	Reviewer	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Pelvic lymph nodes (N=252)	1	41.9% (30, 54)	97.9% (95, 99)	86.7% (70, 95)	83.8% (79, 89)
	2	30.6% (19, 42)	98.9% (96, 100)	90.5% (70, 99)	81.4% (76, 86)
	3	40.3% (28, 53)	96.3% (94, 99)	78.1% (64, 92)	83.2% (78, 88)
Pelvic lymph nodes excluding subjects with a max. lesion size ≤5mm (N=225)					
Prostate gland (N=247)	1	98.0% (95, 99)	0	100% (98, 100)	0
	2	98.0% (95, 99)	0	100% (98, 100)	0
	3	94.3% (91, 97)	0	100% (98, 100)	0

- *Specificity met the pre-specified lower limit of 80%; sensitivity did not meet the 40% pre-specified lower limit in all evaluable subjects*
- *^{18}F-DCFPyL PET/CT showed high PPV and NPV in all evaluable subjects*

- *98% sensitivity and 100% PPV in the prostate gland*

Sub-analysis: Lymph nodes above the PET resolution (>5mm)

Pelvic lymph nodes[1]	Reader	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All subjects (N=252)	1	41.9% (30, 54)	97.9% (95, 99)	86.7% (70, 95)	83.8% (79, 89)
	2	30.6% (19, 42)	98.9% (96, 100)	90.5% (70, 99)	81.4% (76, 86)
	3	40.3% (28, 53)	96.3% (94, 99)	78.1% (64, 92)	83.2% (78, 88)
Excluding subjects with lymph node lesions ≤5mm (N=225)	1	62.9% (47, 79)	97.9% (95, 99)	84.6% (66, 94)	93.5% (90, 97)
	2	48.6% (32, 65)	98.9% (96, 100)	89.5% (67, 98)	91.2% (87, 95)
	3	60.0% (44, 76)	96.3% (94, 99)	75.0% (59, 91)	92.9% (89, 97)

[1] Patient-level analysis

- *Sensitivity and specificity both meet the endpoint success criteria*
- *High PPV and NPV preserved*

Herlemann *et al. Eur Urol* 2016; Harisinghani MG *et al*. NEJM 2003. Maurer *et al*. Euro Urol 2016; de Jong IJ et al. *Eur Urol* 2002

Conclusions

- Unprecedented trial design of a prospective, multi-reader, multi-center, controlled trial using histology as the truth standard
- ^{18}F-DCFPyL was safe and well-tolerated
- Reliable for preoperative staging, and highly predictive of pelvic lymph node metastases
- Sensitive and predictive of localizing locoregional recurrence and metastatic lesions
- ^{18}F-DCFPyL PET/CT imaging provides additional reliable information to infer on initial therapy planning