Review of the First PSMA-Targeted PET Imaging Application

Association of Medical Diagnostics Manufacturers

Hayden Honeycutt, PharmD

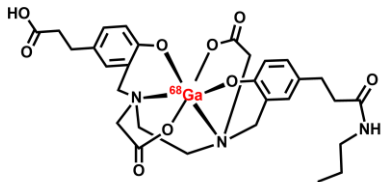
Disclaimer

The views expressed herein represent those of the author and do not necessarily represent the views or practices of the author's employer or any other party.

Overview

- Quick overview of PET and PSMA
- Clinical Data supporting registration
- Registration approach

PET and PSMA definitions

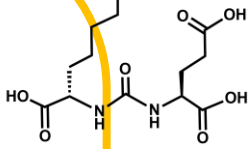


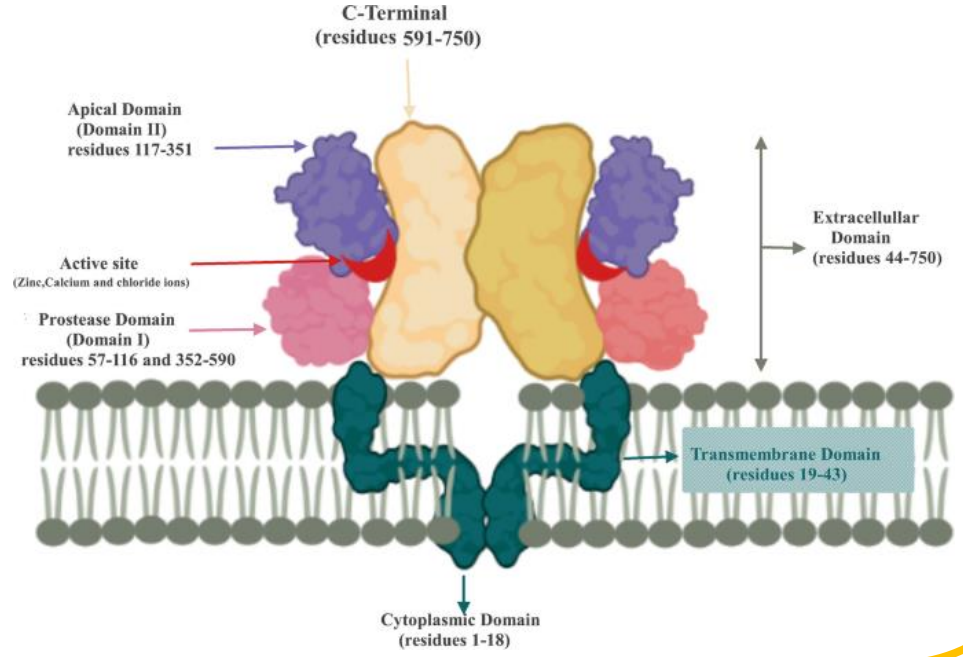
PET

Positron emission tomography (PET) is a technique that measures physiological function by looking at blood flow, metabolism, neurotransmitters, and radiolabelled drugs. [1]

PSMA

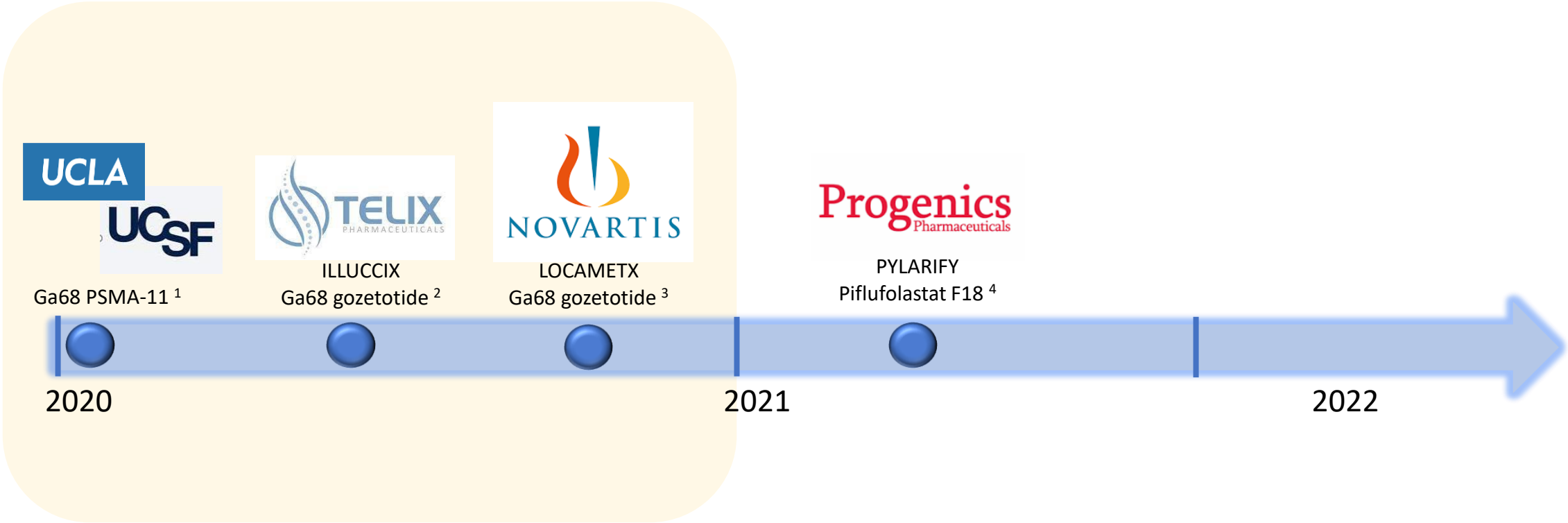
Prostate-specific membrane antigen is a type II transmembrane glycoprotein which is over expressed in prostate cancer [2]





1. Berger. BMJ v326; 2003
2. Nikfarjam et al.Biophysical Reviews 2022:14; 03-315

In 2020, three Ga68 PSMA-11 PET tracers were approved, thanks to the foundational efforts of UCLA & UCSF



1. *Ga68-PSMA-11 Prescribing Info*
2. *Illuccix Prescribing Info*
3. *Locametz Prescribing Info*
4. *Pylarify Prescribing Info*

INDICATION FOR USE[1]

Ga68 PSMA-11 is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- With suspected metastasis who are candidates for initial definitive therapy.
- With suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

1. *Ga68-PSMA-11 Prescribing Info*

KEY CLINICAL STUDY

PC with suspected metastasis before initial definitive therapy[1]

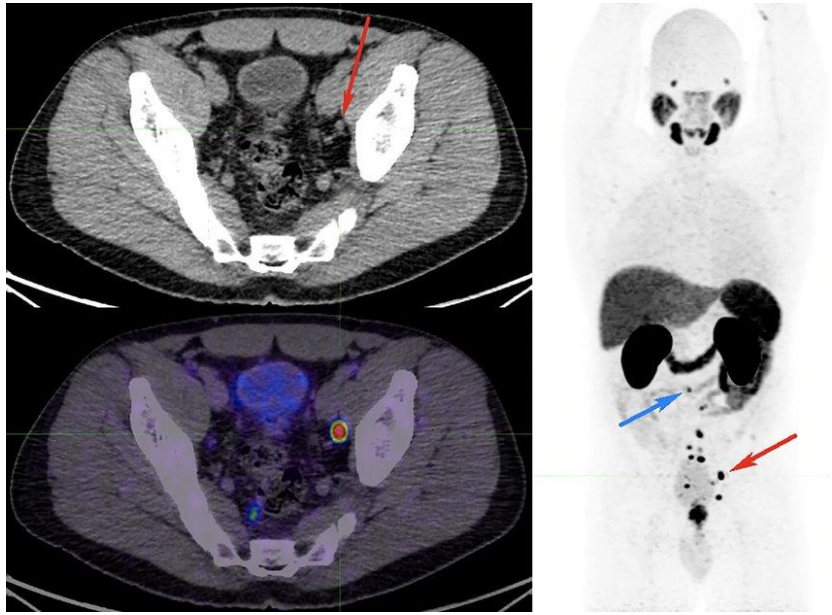
2

Table 5: Patient-Level Performance of Ga 68 PSMA-11 PET for Detection of Pelvic Lymph Node Metastasis* in the PSMA-PreRP Study (n=123)

		Histopathology		Predictive value** (95% CI)
		Positive	Negative	
PET scan	Positive	14	9	PPV 61% (41%, 81%)
	Negative	16	84	NPV 84% (79%, 91%)
Total		30	93	
Diagnostic performance (95% CI)		Sensitivity 47% (29%, 65%)	Specificity 90% (84%, 96%)	

*with region matching where at least one true positive region defines a true positive patient
**PPV: positive predictive value, NPV: negative predictive value

3



1. *Hope et al. JAMA Oncol 2021 Nov; 7(11):1635-1642*
2. *Ga68 PSMA-PET Prescribing Information 2020*
3. *Alipour et al. Ther Adv Med Oncol 2019; 11: 1-14*

KEY CLINICAL STUDY

PC with suspected recurrence based on elevated serum PSA level (BCR)[1]

1

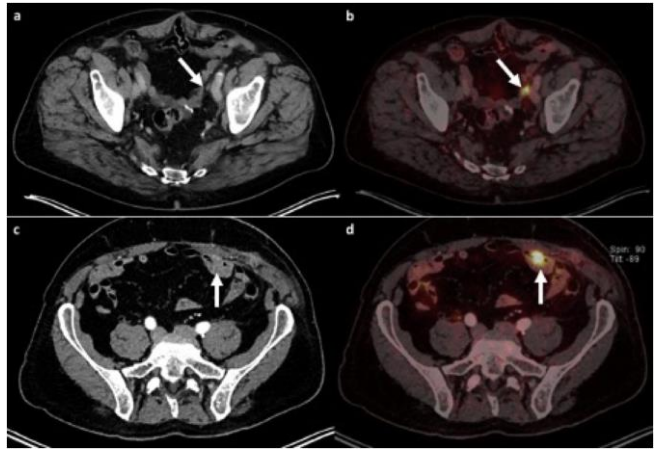
Validation Group	Total Regions/ Patients, No.	No. (%) Confirmed	No. (%) Ruled Out	PPV or SE (95%CI)
Positive Predictive Value				
Composite validation				
PET positive (per-patient)	217	200 (92)	17 (8)	0.92 (0.88-0.95)
PET positive (per-region)	249	229 (92)	20 (8)	0.92 (0.88-0.95)
Histopathologic validation				
PET positive (per-patient)	87	73 (84)	14 (16)	0.84 (0.75-0.90)
PET positive (per-region)	90	76 (84)	14 (16)	0.84 (0.76-0.91)
Sensitivity				
Histopathologic findings				
Confirmed (per-patient)	79	73 (92)[a]	6 (8)[b]	0.92 (0.84-0.96)
Confirmed (per-region)	84	76 (90)[a]	8 (10)[b]	0.90 (0.82-0.95)

Table 6: Patient-Level Ga 68 PSMA-11 PET Results and Percent PET Positivity Stratified by Serum PSA Level in the PSMA-BCR Study (n=628)*

2

PSA (ng/mL)	PET positive patients				PET negative patients	Percent PET positivity*** (95% CI)
	Total	TP**	FP**	Without reference standard		
		With reference standard				
<0.5	48	11	1	36	87	36% (27%, 44%)
		12				
≥0.5 and <1	44	15	3	26	35	56% (45%, 67%)
		18				
≥1 and <2	71	29	1	41	15	83% (75%, 91%)
		30				
≥2	299	137	13	149	29	91% (88%, 94%)
		150				
Total	462	192	18	252	166	74% (70%, 77%)
		210				

*7 patients were excluded from this table due to protocol deviations
**TP: true positive, FP: false positive
***Percent PET positivity = PET positive patients/total patients scanned



3

1. *Fendler et al, JAMA Oncol 2019: 5(6): 856-863*
2. *Ga68-PSMA-PET Prescribing Information 2020*
3. *Morawitz et al, European Journal of Radiology 136 (2021)*

UCLA and UCSF took a unique approach to registration[1]

- Both institutions would submit separate NDAs sharing same clinical and nonclinical information, similar labeling information, but with site-specific CMC modules
- Both submissions would be 505(b)(2) NDAs, referencing published literature for nonclinical and clinical pharmacology and clinical dosimetry
- Both NDAs waived market exclusivity, so the PET imaging providers can submit ANDA immediately, using either NDA drug product as a reference drug
- Academic institutions are indispensable for regulatory approval of PET drugs; while regular drug development and commercialization depends nearly exclusively on industry sponsorship

1. Carlucci et al, JNM,2020.

From academic NDA to commercial utility[1]

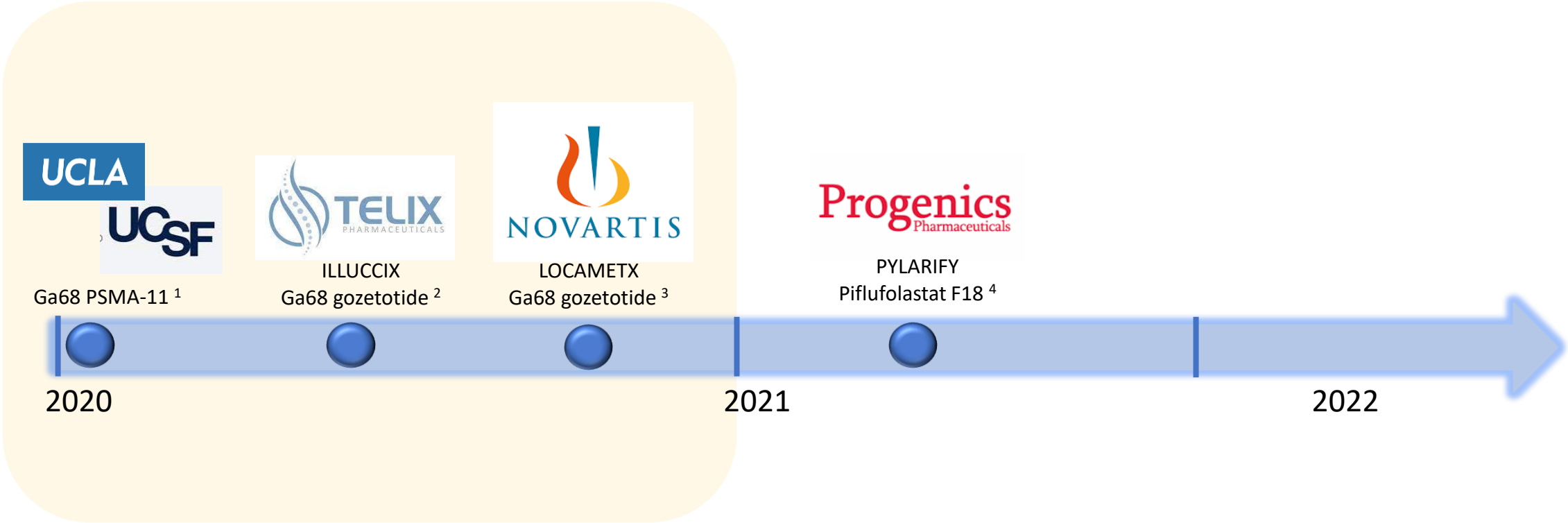
- In Oct 2020, the FDA published a guidance document titled “Referencing Approved Drug Products in ANDA Submissions”
- An ANDA submission will most likely include:
  - Module 1 (administration and labeling)
  - Module 2 (Common Technical Document (CTD) summary)
  - Module 3 (CMC information)

- Section 1.12.12 requires information demonstrating that the generic product is the same as the reference drug by demonstrating the active ingredients, route of administration, dosage form, strength and conditions of use are the same as those of the reference drug

- Both TELIX and Novartis filed an ANDA cross-referencing UCLA/UCSF’s NDA

1. Carlucci et al, JNM,2020.

In 2020, three Ga68 PSMA-11 PET tracers were approved, thanks to the foundational efforts of UCLA & UCSF



1. *Ga68-PSMA-11 Prescribing Info*
2. *Illuccix Prescribing Info*
3. *Locametz Prescribing Info*
4. *Pylarify Prescribing Info*

The PIs contain similar indications but differences in dosage, strength and preparation[1,2,3]

UCLA UCSF

Gallium Ga 68 PSMA-11 Injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
Ga 68 PSMA-11 Injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
• with suspected metastasis who are candidates for initial definitive therapy.
• with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. (1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: clear, colorless solution in a multiple-dose vial containing 18.5 MBq/mL to 185 MBq/mL (0.5 mCi/mL to 5 mCi/mL) Ga 68 PSMA-11 at calibration time (3)

TELIX PHARMACEUTICALS

ILLUCCIX (kit for the preparation of gallium Ga 68 gozetotide[§] injection), for intravenous use
Initial U.S. Approval: 2020
([§]Gozetotide is also known as PSMA-11)

INDICATIONS AND USAGE
ILLUCCIX, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:
- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. (1)

DOSAGE FORMS AND STRENGTHS
ILLUCCIX is supplied as a kit containing:
- Vial 1 (Gozetotide Vial) contains 25 mcg gozetotide and 10 mcg D-mannose (stabilizer) as a lyophilized powder
- Vial 2 (Acetate Buffer Vial) contains acetate buffer, either:
  - Vial 2A in Configuration A for use with cyclotron produced Ga 68 via GE FASTlab™ or EZAG generator
  - Vial 2B in Configuration B for use with IRE generator
- Vial 3 (Sterile Vacuumed Reaction Vial) for the collection of gallium Ga 68 chloride and radiolabeling reaction.

After radiolabeling and pH adjustment with acetate buffer and radiolabeling with Ga 68, Vial 3 is a multiple-dose vial containing up to 1,850 MBq (50 mCi) of Gallium Ga 68 Gozetotide Injection in 7.5 mL at a strength of up to 247 MBq (6.7 mCi) per mL. (3)

NOVARTIS

LOCAMETZ® (kit for the preparation of gallium Ga 68 gozetotide injection), for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
LOCAMETZ, after radiolabeling with gallium-68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer:
- with suspected metastasis who are candidates for initial definitive therapy.
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.
- for selection of patients with metastatic prostate cancer, for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. (1)

----------DOSAGE FORMS AND STRENGTHS----------
- Kit for the preparation of gallium Ga 68 gozetotide injection supplied in a multiple-dose vial containing 25 mcg of gozetotide as a white lyophilized powder. After radiolabeling with gallium-68, the vial contains a sterile solution of gallium Ga 68 gozetotide at a strength up to 1,369 MBq (37 mCi) in up to 10 mL at calibration date and time. (3)

1. *Ga68-PSMA-11 Prescribing Info*
2. *Illuccix Prescribing Info*
3. *Locametz Prescribing Info*

Summary

- 68Ga-PSMA-11 is a PET radiotracer that targets PSMA receptors, overexpressed in advanced prostate cancer
- UCLA/UCSF, in collaboration with the FDA, obtained the approval of the first PSMA-targeted PET tracer
- Market exclusivity was lifted allowing industry and other research hospitals to file ANDAs, supporting commercialization and distribution for widespread patient care
- This is an example of the critical role Academia can play in bringing novel tracers to the market