PSMA Imaging in Prostate Cancer Care

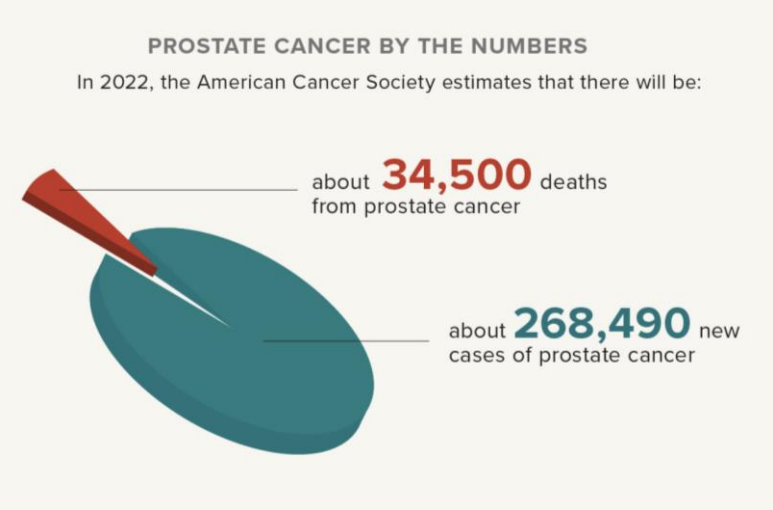
Disclaimer

The information presented is provided by Telix Pharmaceuticals as a request by IPCSG

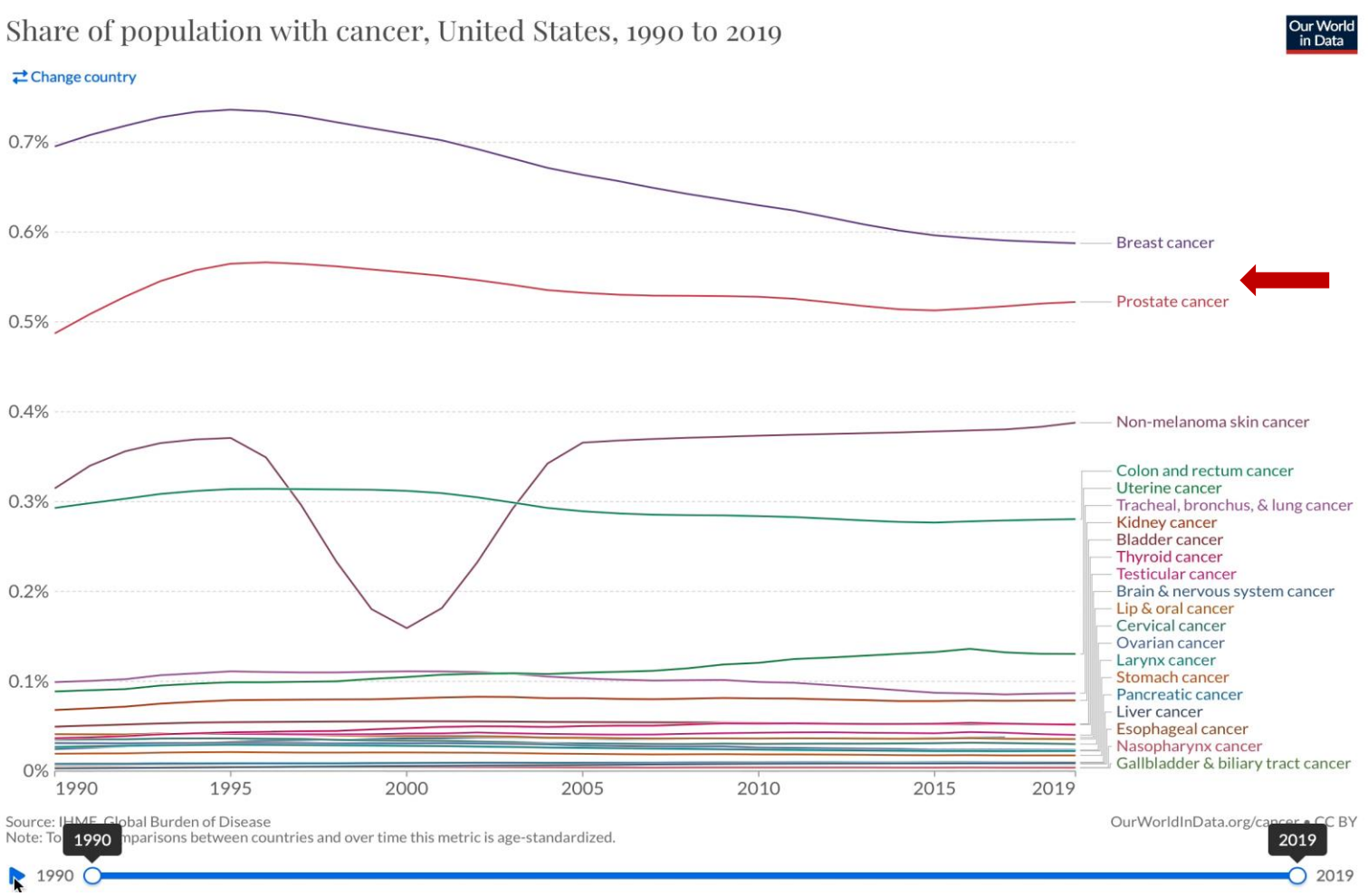
Prostate Cancer Prevalence in the US[1]:

PCa is the most commonly diagnosed cancer in men[2]:

- 13.1% of all new cancers*
- 5.6% of all cancer deaths*



Graphic Resource: healthline: a Prostate Cancer Roadmap[3]



*male and female 1. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program Cancer Statistics. Cancer stat facts: Prostate Cancer. 2. https://ourworldindata.org/cancer ; 3. https://www.healthline.com/health/advanced-prostate-cancer/prostate-cancer-treatment-a-typical-journey

Risk and Survival

Some men are at higher risk for Prostate Cancer

- **Most frequently diagnosed among men aged 65 – 74[1]**
- **African Americans are 1.8x more likely to be diagnosed and 2.2x more likely to die than White men**
- **Veterans are 2.4x greater incidence rate of PCa than the general public**

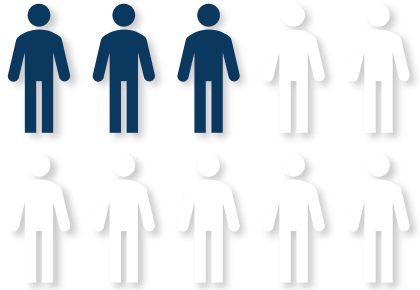
About **1 in 8** men will be diagnosed with prostate cancer during their lifetime

6 in 10 cases of prostate cancer are diagnosed in men who are 65 and older

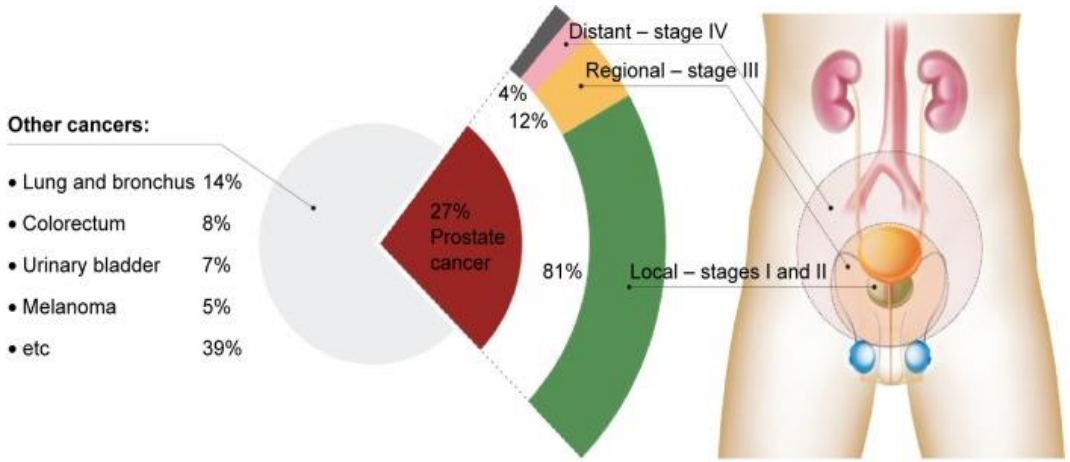
Stage at diagnosis is a strong predictor of the length of survival[3]

The 5-year survival rate for local or regional prostate cancer is nearly **100%**

However, for prostate cancer that has spread to other parts of the body (distant), the 5-year survival rate is **30%**

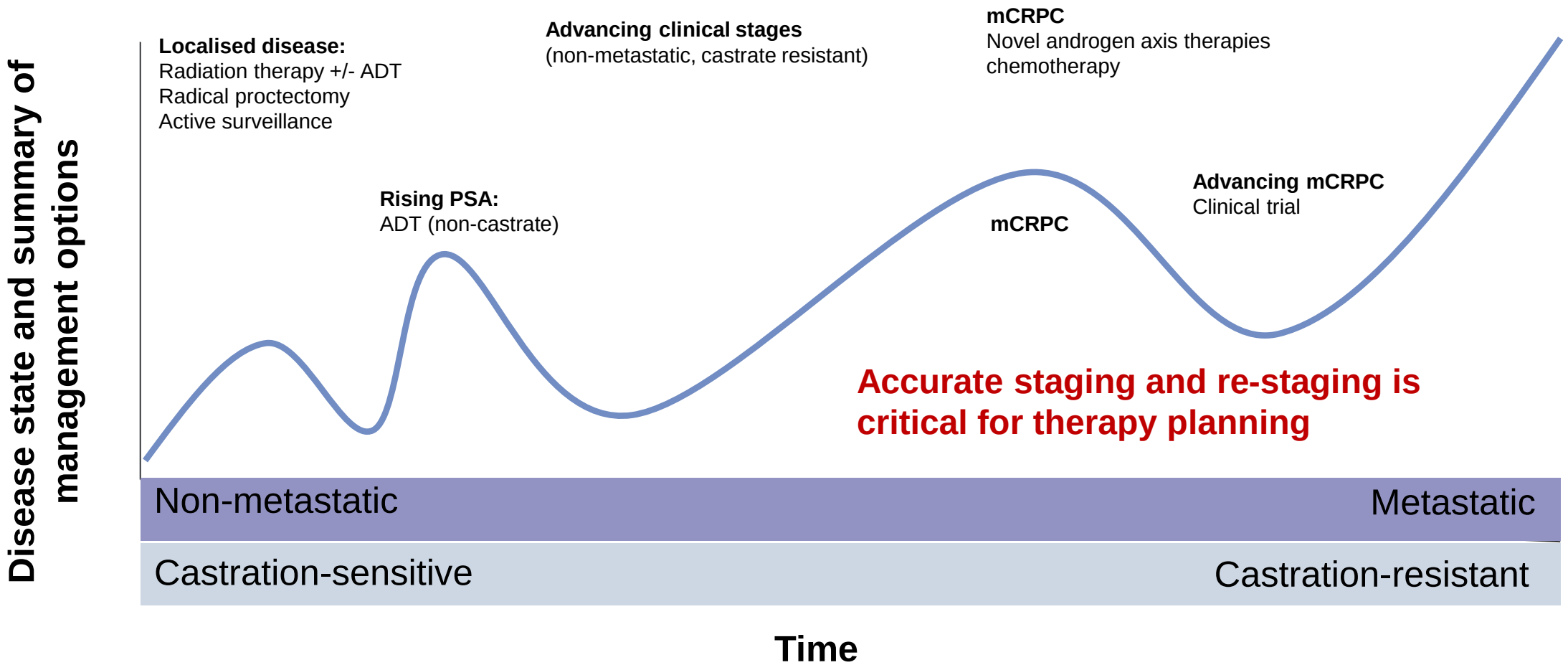


Although large percentage of diagnosis is at local or regional stage, patients diagnosed with metastatic prostate cancer increased from 4% to 8% between 2003 and 2017[3]



1. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program Cancer Statistics. Cancer stat facts: Prostate Cancer. https://seer.cancer.gov/statfacts/html/prost.html. Accessed November 2021 2. Urology Times Journal, Vol 48 No 11, Volume 48, Issue 11; 4. . Cancer.net. Prostate Cancer: Statistics. https://www.cancer.net/cancer-types/prostate-cancer/statistics. Accessed November 2021. 5. Graphic from Kang BJ, Int J Nanomedicine. 2015;10 6555-6569.

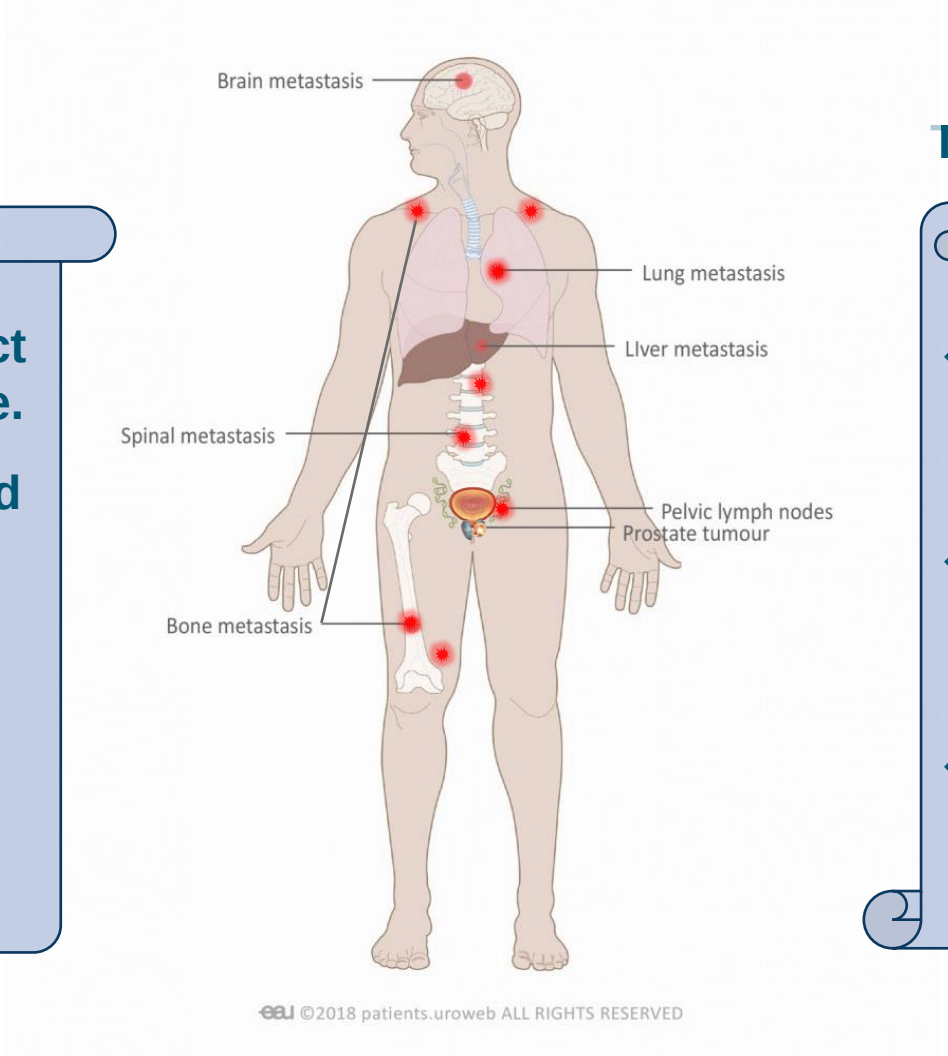
Prostate Cancer Progression



Imaging Plays an Important Role in Prostate Cancer Management

At Initial Staging

- Noninvasively detect and localize disease.
- Confirm grading and staging;
- Help avoid overtreatment
- Help prevent undertreatment



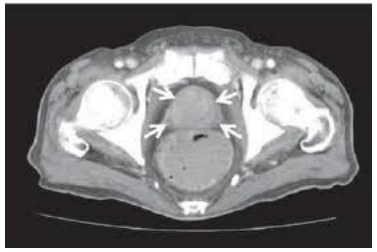
Throughout Management

- Confirm treatment effectiveness (local or systemic)
- Consistently monitoring progression
- Detect and localize recurrence

Imaging in Prostate Cancer Management

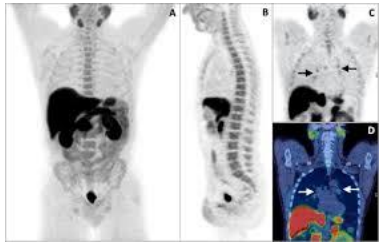
Computed Tomograph (CT):

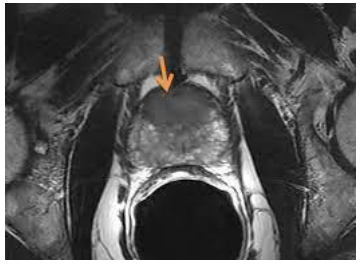
Conventional, well established, can be fast for whole body , **but** poor sensitivity and specificity.

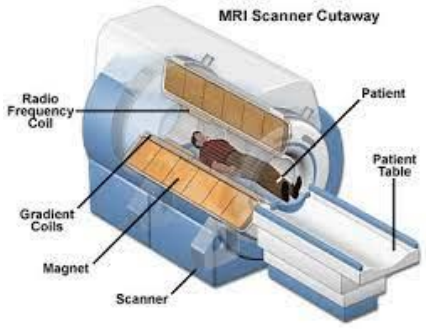


PET Scan:

3D, highly sensitive, targeting active tumor cells, can be very specific with the right target .





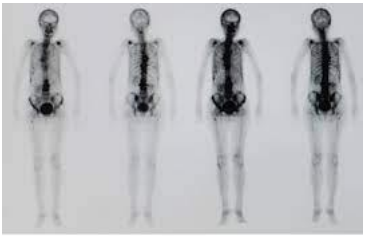


Magnetic Resonance Imaging (MRI):

High resolution and very good for soft tissue lesions in and out of prostate, **but** not good for bone, costly and limited imaging field.

Bone scintigraphy:

2D, fast, detect bone lesion , **but** not specifically Prostate cancer bone lesion and low resolution.



Challenges of Conventional Imaging Techniques

Guidelines recommend conventional imaging methods,[1] but bone scans and CTs result in positive findings in less than 10% of men with biochemical recurrence, particularly those lesions that are less than 1 cm in size with PSA <20 ng/mL[2-6,9]

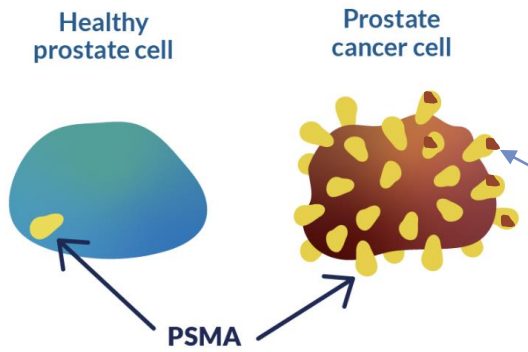
Modality	Standard Use	Challenges
Bone scintigraphy (BS)	• Widely available[7] • Identify bony lesions[7]	• False positives in asymptomatic disease ; limited accuracy for low PSA[1,8]
Computed tomography (CT)	• Use to monitor treatment response (soft tissue/lymph nodes/viscera)[8] • Can detect sclerotic bone and visceral metastases[8]	• Less accurate detecting local recurrence(post RP)[8] • Dependent on size for nodal evaluation, which confers poor sensitivity[8]
Multiparametric magnetic resonance imaging (mpMRI) or standard MRI	• Identification of extra-prostatic margins/recurrence post-radiation therapy (RT)[8]	• Limited utility in staging pelvic lymph nodes[8]

cm = centimeter; CT = computer tomography; mL = milliliter; ng = nanogram; PSA = prostate-specific antigen; RP = radical prostatectomy

The advent of highly accurate imaging techniques could lead to cost savings in the management of PCa

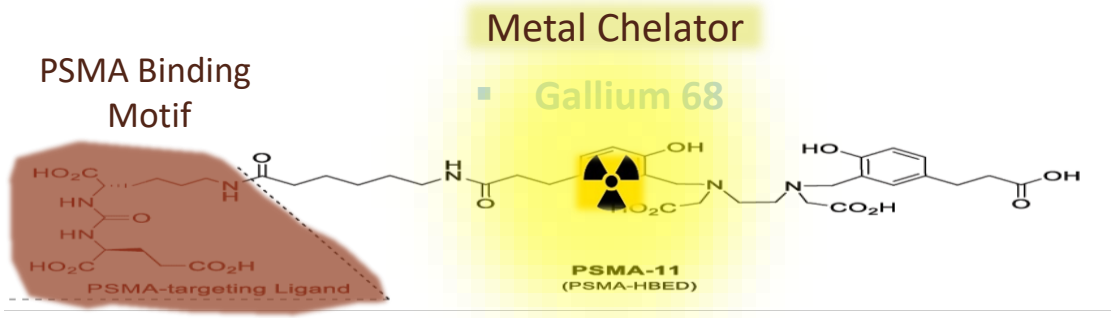
1. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer V2.2021 2. Choueiri TK et al. *J Urol.* 2008 3. Hricak H et al. *Radiology.* 2007 4. Ikonen S et al. *J Urol.* 1998 5. Kirkham AP et al. *Eur Urol.* 2006 6. Merdan S et al. *Urology.* 2014 7. Messiou C et al. *Br J Cancer.* 2009 8. Froemming AT et al. https://acsearch.acr.org/docs/69369/Narrative. 9. Alipour R, et al. Ther Adv Med Oncol. 2019

Prostate-specific membrane antigen (PSMA) Based PET Imaging

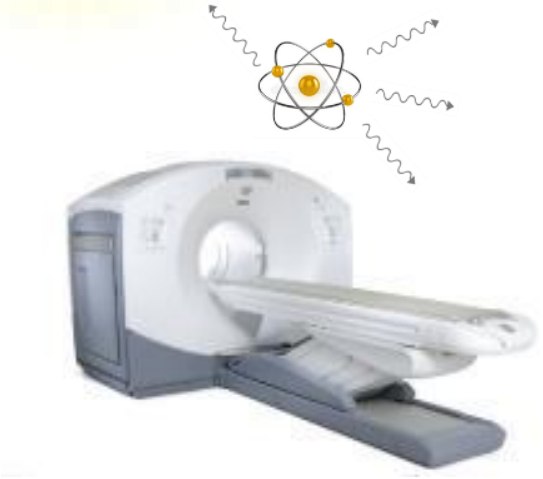


- A protein that is abundant on the surface of prostate cancer cells.
- This is what makes PSMA a good target for prostate cancer imaging
- PSMA is also found on cancer cells that have spread to other parts of the body, like the lymph nodes or bones

PSMA-11 is a small molecule that can bind PSMA with high specific and affinity with a metal chelator



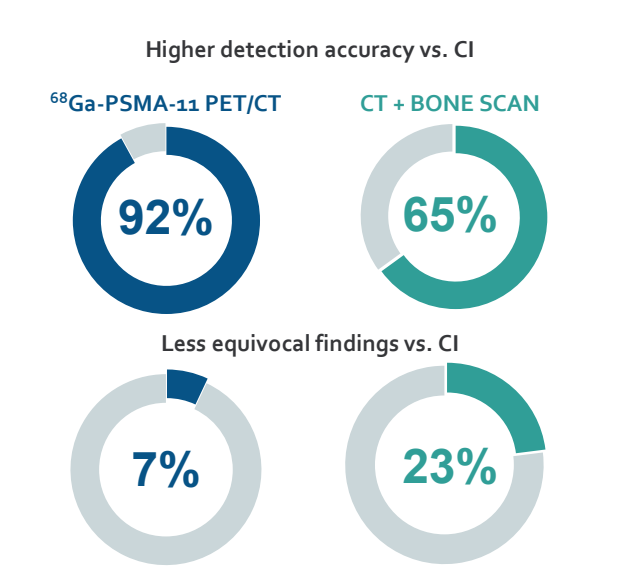
PET MOLECULAR IMAGING



Greater Detection of metastatic disease with ^{68}Ga-PSMA-11 PET/CT vs Conventional Imaging Initial Staging

PSMA PET/CT is a suitable replacement for conventional imaging, providing superior accuracy compared to CT and bone scanning[1]

- 27% superior detection accuracy compared to CI
- Superiority in detecting small-volume nodal or visceral disease and early bone metastases
- Fewer equivocal findings

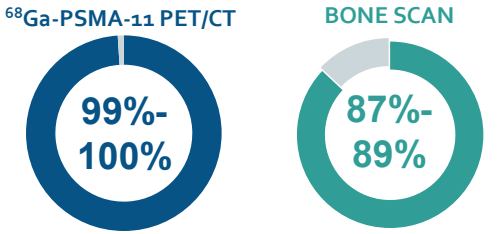


Prospective randomized study of biopsy-proven, high-risk prostate cancer at initial staging (n=302)

1. Hofman M.S., et al. *Lancet*. 2020

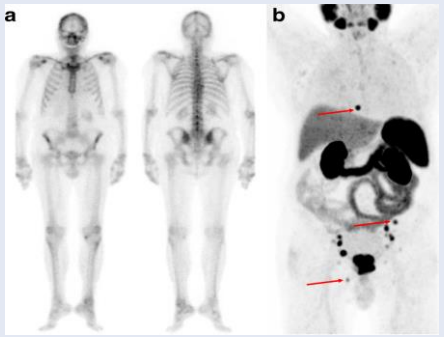
^{68}Ga-PSMA-11 PET/CT vs Bone scan (n=126)

^{68}Ga-PSMA-11 increased the diagnostic sensitivity of bone metastases >10% compared to bone scan[2]



2. Pyka T, et al. *Eur J Nucl Med Mol Imaging*. 2016

^{68}Ga-PSMA-11 revealed metastases in 10% of patients (intermediate to high-risk PCa) classified as Mo on bone scan.[3,4]



A. Patient (PSA 44 ng/mL, Gleason score 9, T#3) classified as no bone metastasis (Mo) according to initial bone scan (anterior and posterior projection).

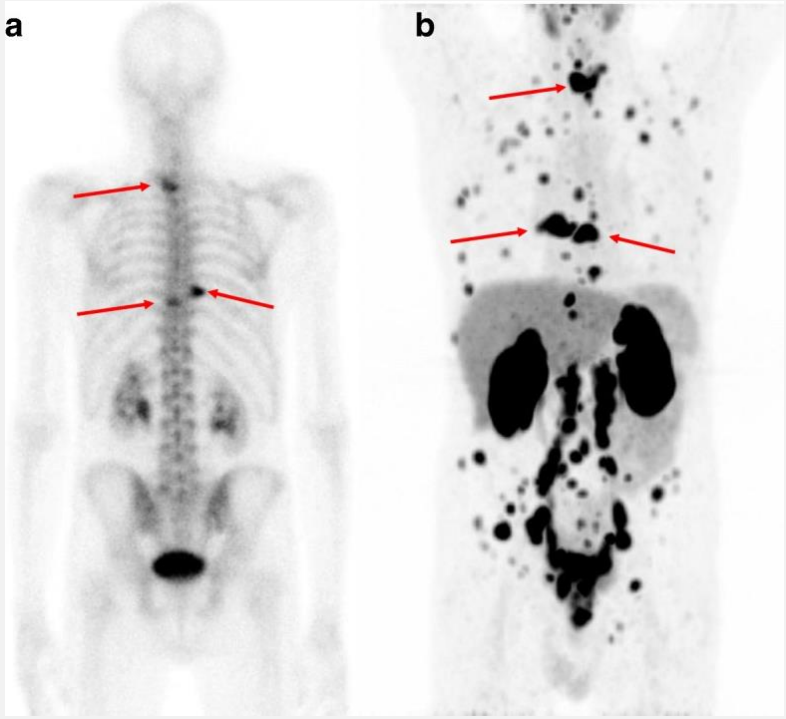
B. ^{68}Ga-PSMA-11 PET/CT revealed several lesions with PSMA uptake, including 3 bone metastases (arrows).

3. Zacho HD, et al. *EJNMMI Research*. 2020 4. Wu H et al. *World J Mens Health*. 2020

CT = computed tomography; Ga = gallium; MRI = magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

Greater Detection of metastatic disease with ^{68}Ga-PSMA-11 PET/CT vs Bone Scan

^{68}Ga-PSMA-11 PET/CT exhibited few equivocal bone findings and revealed bone metastases in patients with newly diagnosed PCa and negative BS results.[1]

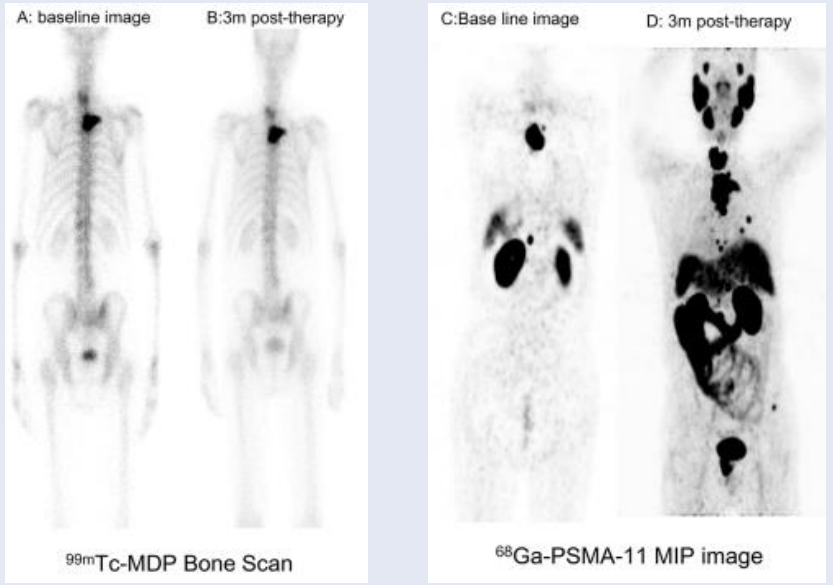


Patient (PSA 8 ng/mL, Gleason score 9, T3)

A. Three bone metastases on BS (red arrows)
B. ^{68}Ga-PSMA-11 PET/CT MIP revealed numerous bone lesions and lymph nodes in the pelvis and abdomen. (red arrows indicate the bone metastases also shown by BS)

1. Zacho HD, et al. *EJNMMI Research*. 2020

68Ga-PSMA-11 PET/CT has utility for M staging and can be used for risk stratification and selection of treatment strategy.[2]

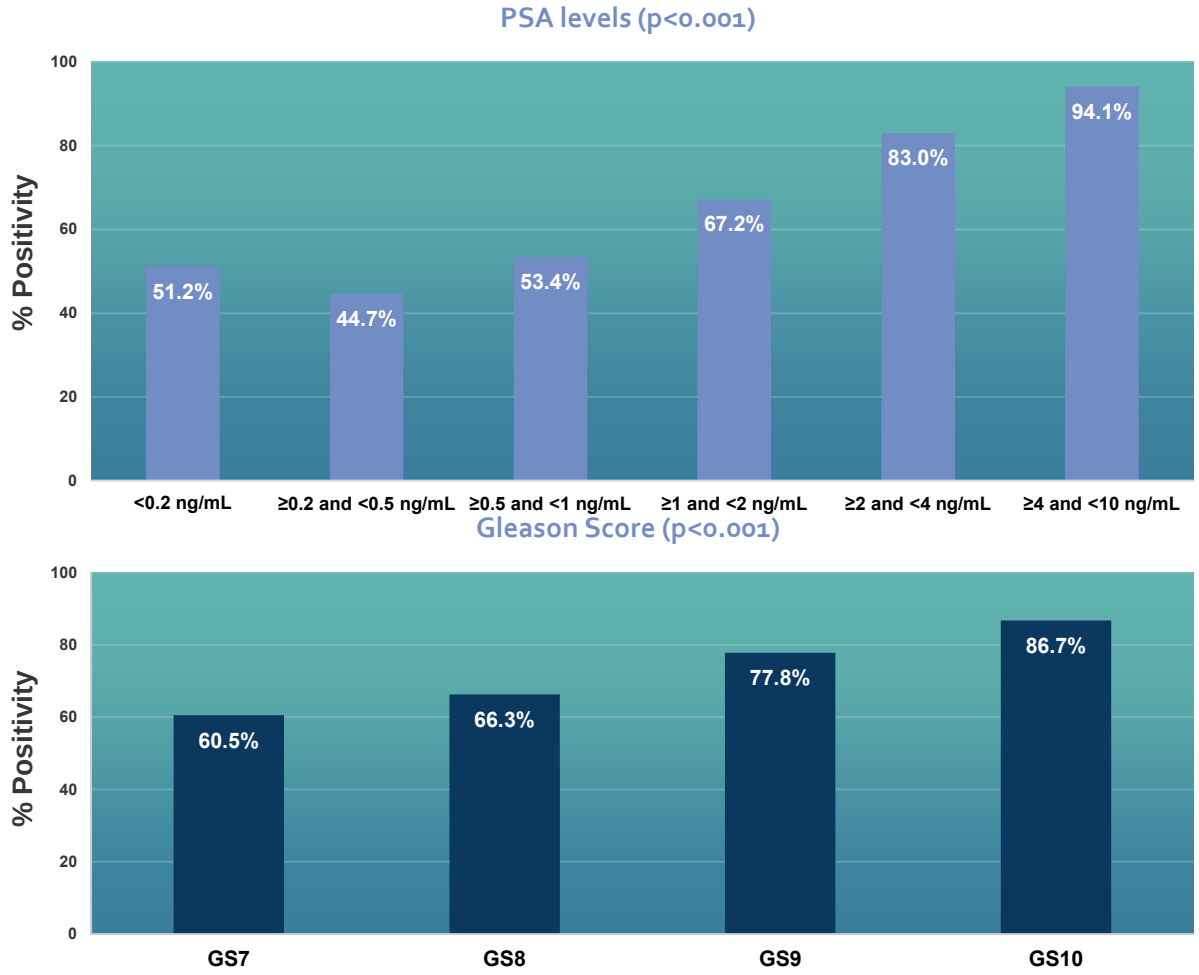


Serial 68Ga-PSMA-11 images in a case with progressive mCRPC.
A & B. Bone scan showing no changes in a patient with mCRPC after ADT therapy.
C & D. 68Ga-PSMA-11 PET/CT MIP revealed multiple metastases and progression compared to a baseline image.

2. Zang, S et. al. Oncotarget (2017

CT = computed tomography; Ga = gallium; MRI = magnetic resonance imaging; BS = Bone Scan; MIP = maximum image projection; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; mCRPC = metastatic castrate resistant prostate cancer

^{68}Ga-PSMA-11 PET/CT Detection of Biochemical Recurrence



PSMA-PET/CT positivity significantly correlate to PSA values [3-6]
Multiple studies have shown 63%-75% positive rate, much improved from that of Auxumin[6]

PSMA PET/CT was found to be reliable in the workup of PCa patients with biochemical recurrence, and possible local and metastatic recurrence[6]

- **Factors associated with a positive PSMA-PET/CT, include:**
  - **Gleason score**
  - **PSA at PET**
  - **PSA doubling time and RT as primary treatment**

BCR = biochemical recurrence; CT = computed tomography; Ga = gallium; MRI = magnetic resonance imaging;PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; GS = Gleason score; mL = milliliter; ng = nanograms; PCa = prostate cancer

^{68}Ga-PSMA-PET provides a high diagnostic value in biochemically recurrent PCa

1. Hoffmann MA, et al. *Cancers*. 2020 2. Afshar-Oromieh A, et al. *J Nucl Med Mol Imaging*. 2017 3. Fendler WP, et al. *JAMA Oncol*. 2019 4. Eiber M, et al. J Nucl Med. 2015 5. Calais J et al. *Lancet Oncol*. 2019 6. Cerci JJ et al. *J Nucl Med*. 2021 7. Abghari-Gerst M., et al. *J Nuc Med*. 2021

^{68}Ga-PSMA impacts Prostate Cancer management in real world

^{68}Ga-PSMA-11 is the **most widely used** radiotracer used for PET imaging of prostate cancer[1]

^{68}Ga-PSMA-11 guided management changes in

up to 43%	up to 68%	up to 70%
Intermediate-High Risk Males at Initial Staging[2-5]	Males at **BCR**[6,7]	Males at **mCRPC**[8]

1. Kurash, et al. *Sci Rep* **10,** 3109 (2020). **2.** Sonni I, et al. *J Nucl Med*. 2020;61(8):1153-1160. **3**. Roach PJ, et al *J Nucl Med.* 2018;59(1):82-88. **4.** Hofman MS, et al. *Lancet*. 2020;395(10231):1208-1216. **5.** Grubmuller B, et al. *Clin Cancer Res.* 2018;24(24):6300-6307. **6.** Calais J, et al. J Nucl Med. 2018 Mar;59(3):434-441. **7**. Koerber SA, et al. *J Nucl Med*. 2018;60(2):234-240. **8.** Fourquet A, et al. *Sci Rep.* 2020;10:2104.

^{68}Ga-PSMA-11 Changes in Patient Management

In randomized studies of biopsy-proven, high-risk PCa, ^{68}Ga-PSMA-11 was found to influence management changes by up to 43% of patients at primary staging[1-3]

Management changes were implemented almost 2X more often with ^{68}Ga-PSMA-11 vs. conventional imaging[4]

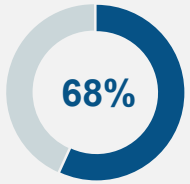
Patient Management Changes
Primary Staging and BCR

Initial Staging[4]

^{68}Ga-PSMA-11 PET/CT (n=41)

CT + BONE SCAN (n=23)

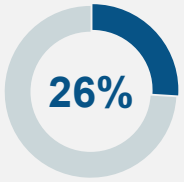
Biochemical Recurrence[5]



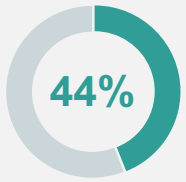
^{68}Ga-PSMA-11 PET/CT (n=12,800)

In an analysis of tumor classification and radiotherapeutic management with ^{68}Ga-PSMA-11 vs conventional imaging:[6]

^{68}Ga-PSMA-11 changed tumor classification and radiotherapeutic plan of treatment-naïve patients



of patients with a change in tumor classification (n=121)



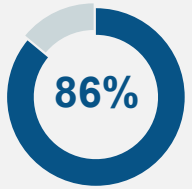
of patients with a change in radiotherapeutic plan (n=62)

1. Sonni I, et al. *J Nucl Med*. 2020 2. Roach PJ, et al. *J Nucl Med*. 20183. Grubmuller B, et al. *Clin Cancer Res*. 2018 4. Hofman M.S., et al. *Lancet*. 2020 5. Calais J, et al. *J Nucl Med*. 2018 6. Koerber SA, et al. *J Nucl Med*. 2019

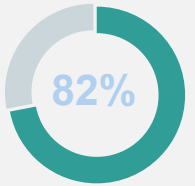
In randomized studies of patients with metastatic PCa, ^{68}Ga-PSMA-11 PET/CT was found to influence[1-3]

Patient Management Changes
Metastatic Prostate Cancer (PCa)

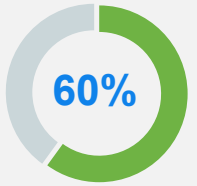
Change in Staging[1] (n=22)



Change in Management[2] (n=43)

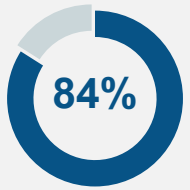


Disease Management Changes PSA < 2ng/mL[3] (n=10)

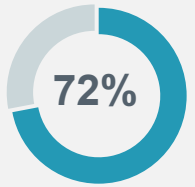


In patients restaged with advanced or metastatic disease, ^{68}Ga-PSMA-11 had:[1,2]

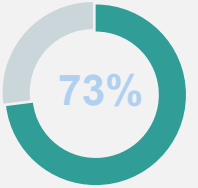
Detection Rate[1] (n=197)



Impacted Patient Management[1] (n=18)



Influenced subsequent treatment choice[2] (n=33)



1. Sonni I, et al. *J Nucl Med*. 2020 2. Kuten J, et al. *EJNMMI Res*. 2019 3. Fourquet A, et al. *Sci Rep*. 2020

CT = computed tomography; Ga = gallium; MRI = magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

Illuccix® for PSMA-11 Labeling

Illuccix® is approved by U.S. FDA (Dec. 20th, 2021) and by Australian TGA (Nov. 1st. 2021) for PSMA Imaging in Prostate Cancer

Indications and Usage

Illuccix®, 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

Important Safety Information

Warnings and Precautions

Risk for Misdiagnosis

Image interpretation errors can occur with gallium-68 gozetotide PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of gallium-68 gozetotide for imaging of biochemically recurrent prostate cancer seems to be affected by serum PSA levels and by site of disease. The performance of gallium-68 gozetotide for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by Gleason score. Gallium-68 gozetotide uptake is not specific for prostate cancer and may occur with other types of cancer as well as non-malignant processes such as Paget's disease, fibrous dysplasia, and osteophytosis. Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended.

Radiation Risks

Gallium-68 gozetotide contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care workers. Advise patients to hydrate before and after administration and to void frequently after administration.

Adverse Reactions

The safety of gallium-68 gozetotide was evaluated in 960 patients, each receiving one dose of gallium-68 gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium-68 gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

Drug Interactions

Androgen deprivation therapy and other therapies targeting the androgen pathway

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, can result in changes in uptake of gallium-68 gozetotide in prostate cancer. The effect of these therapies on performance of gallium-68 gozetotide PET has not been established.

https://illuccix.com/#safety-information

Efficacy established at initial staging

Illuccix® accuracy demonstrated in a pivotal trial with ^{68}Ga-PSMA-11 by histopathology comparison

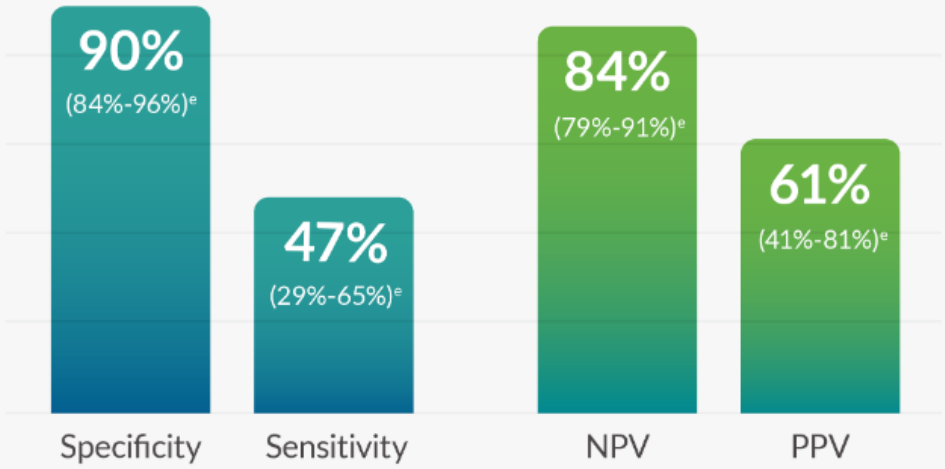
The open-label, prostate-specific membrane antigen-preprostatectomy (PSMA-PreRP) study (N=325) compared majority positron emission tomography (PET) reads to pelvis lymph node histopathology results.[1]

In an exploratory subgroup analysis based on summed Gleason score, there was a numerical trend toward more true positives in patients with a Gleason score of ≥8 compared to those with a Gleason score of ≤7.[1]

In an exploratory analysis of pelvic nodal metastasis in all patients, including those without histopathology reference standard, and using an imputation method[1,c]:

- Imputed sensitivity was 47% (95% CI: 38%-55%)
- Imputed specificity was 74% (95% CI: 68%-80%)

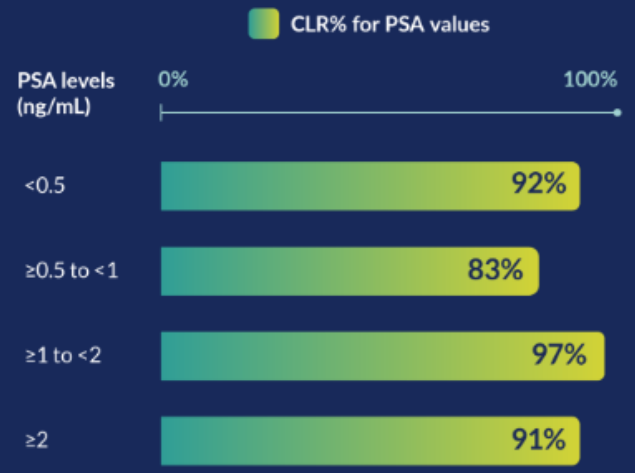
Patient-Level Performance of ^{68}Ga-PSMA-11 for Detection of Pelvic Lymph Node Metastasis (n=123)[1,d]



Among the pool of 6 readers, sensitivity ranged from 36% to 60%, specificity from 83% to 96%, positive predictive value from 38% to 80%, and negative predictive value from 80% to 88%.

Efficacy established at biochemical recurrence (BCR) even at low PSA levels

CLR is defined as the true positive percentage among all positive PET scans[1,h]



In 2 exploratory analyses of gallium Ga 68 gozetotide PET positive patients without reference standard information using an imputation approach[1,i]

- 72% (340/475) were imputed as true positive in one or more regions (95% CI: 68%-76%)
- 54% (340/635) were correctly detected as true positive (95% CI: 50%-57%) among all BCR patients who received a PET scan, whether it was read as positive or negative

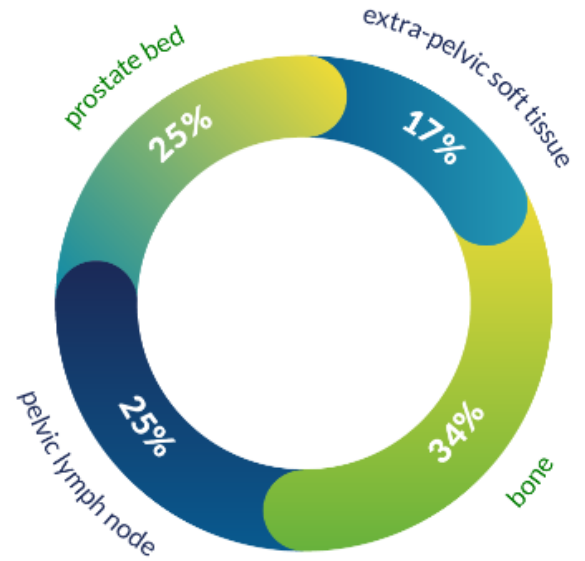
CLR, correct localization rate.

[h]TP/TP+FP.

[i]Using an estimated likelihood that ≥1 location-matched PET positive lesion was reference standard positive based on patient-specific factors.

Illuccix® identified lesions across all vital regions as seen in a pivotal trial with ^{68}Ga-PSMA-11[1,j]

74% of patients (n=469) had ≥1 positive region detected by ^{68}Ga-PSMA-11 PET majority read



[j]Total does not add up to 100% due to rounding of percentages.

View Trial Design

Learn How to Read an Illuccix® Scan

https://illuccixhcp.com/efficacy/#bcr

What to Expect

Hydrate

2 hrs
Prior to Administration

Administer

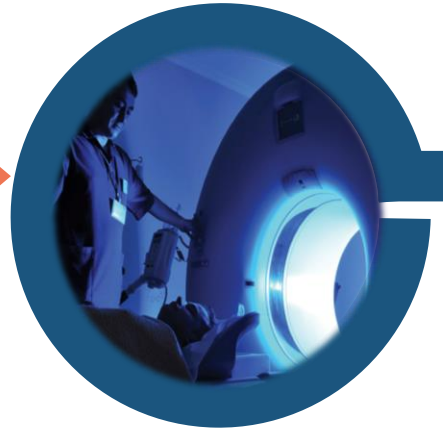
Bolus IV Injection

Void

50 minutes
After Administration

Scan

60 minutes
After Administration



Complete

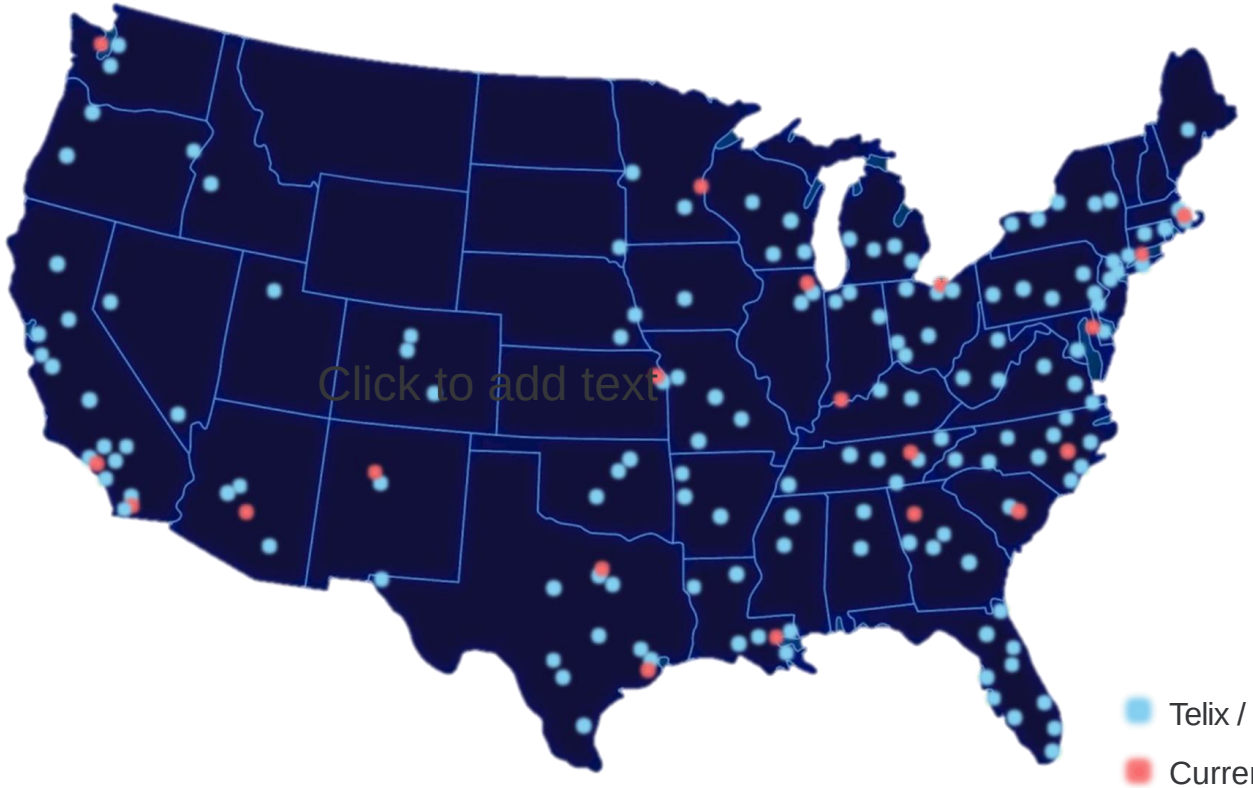
90 minutes
After Administration

Summarized from Telix Illuccix Website for HCP; Illuccix Patient Brochure and Outreaching Medical Materials: https://illuccix.com

Illuccix (TLX591-CDx) PSMA-PET[1] imaging

A differentiated offering in the PSMA-PET market

- **Access** to ~90% of eligible PET sites
- **On-demand** pharmacy-based production with a high yield product
- **Customer** and patient scheduling flexibility



Telix / partner sites

Current competitor sites (4 November 2021)

Illuccix® (Kit for the preparation of ^{68}Ga-PSMA-11) has received marketing authorisation approval in Australia. In all other jurisdictions, including the United States, it is an investigational product and has not attained a marketing authorisation. Product launch in the United States is subject to FDA approval of a New Drug Application (NDA)

Telix: An established global leader in radiopharmaceuticals

Commercial stage company with extensive pipeline of therapeutic and diagnostic assets

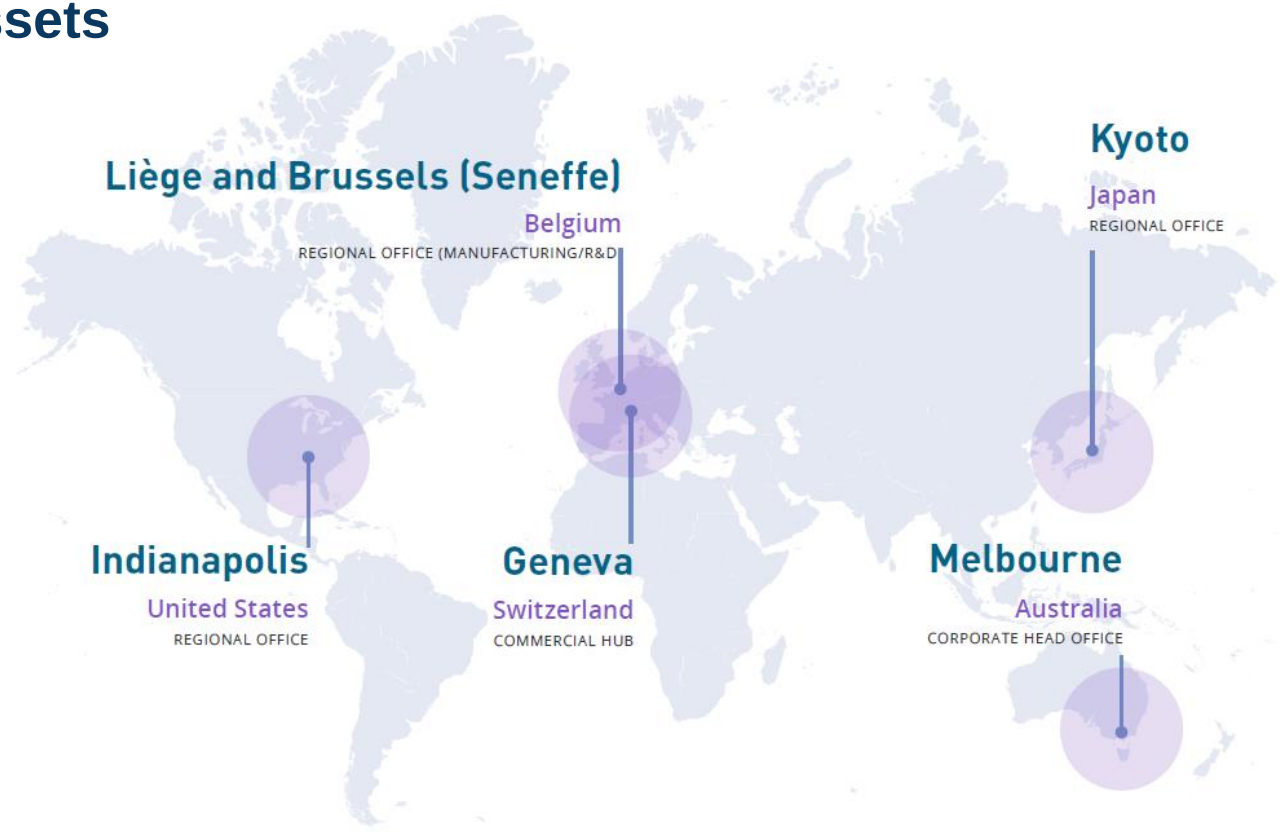
1st FDA approval achieved in late-2021[1]

18 active clinical studies, across 8 indications[2]

Underpinned by a secure global supply chain and distribution network

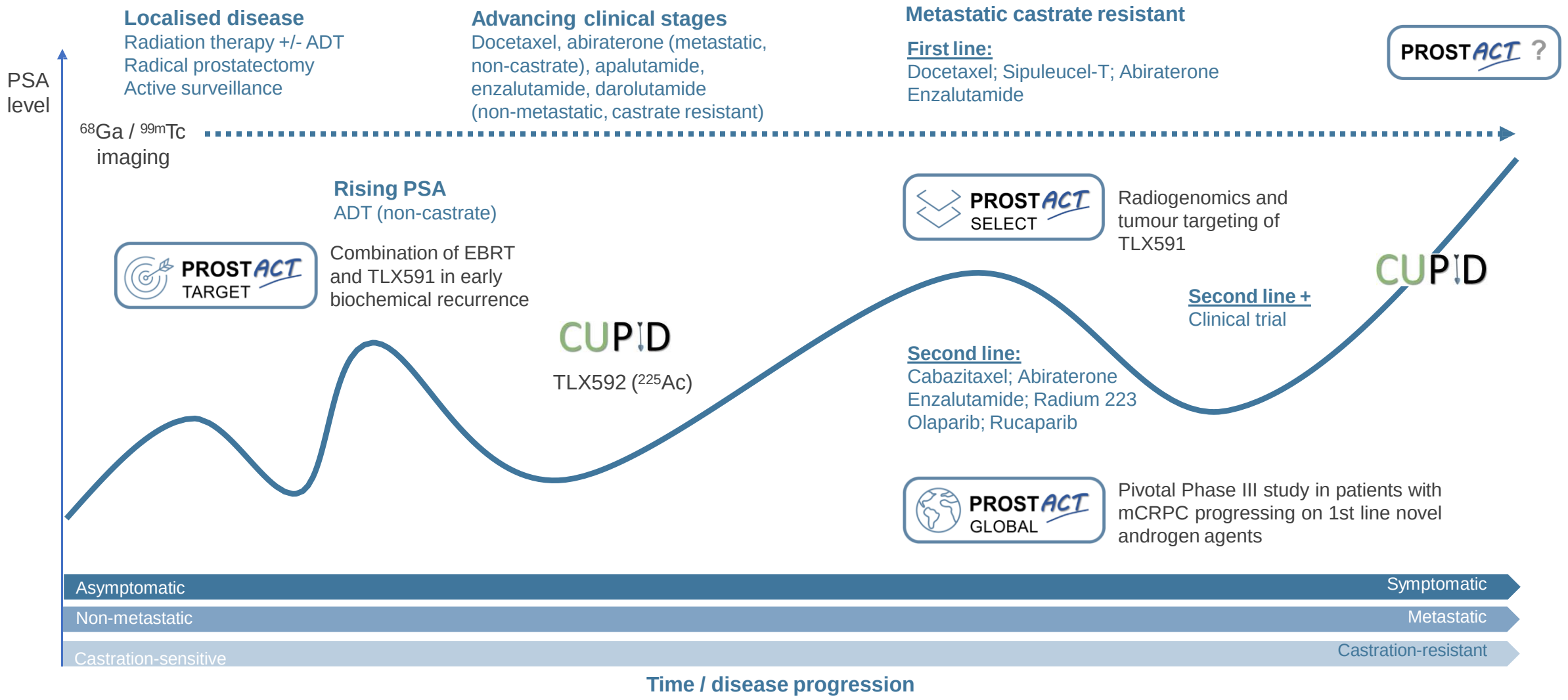
80 countries in the distribution network, enabling access to all major markets across North America, EMEA, APAC and Latin America

11 countries with a manufacturing footprint



1. United States Food and Drug Administration – ASX 20 December 2021.
2. Includes partnered investigator-led studies.

In the Future: Telix Support the patient every step of the way

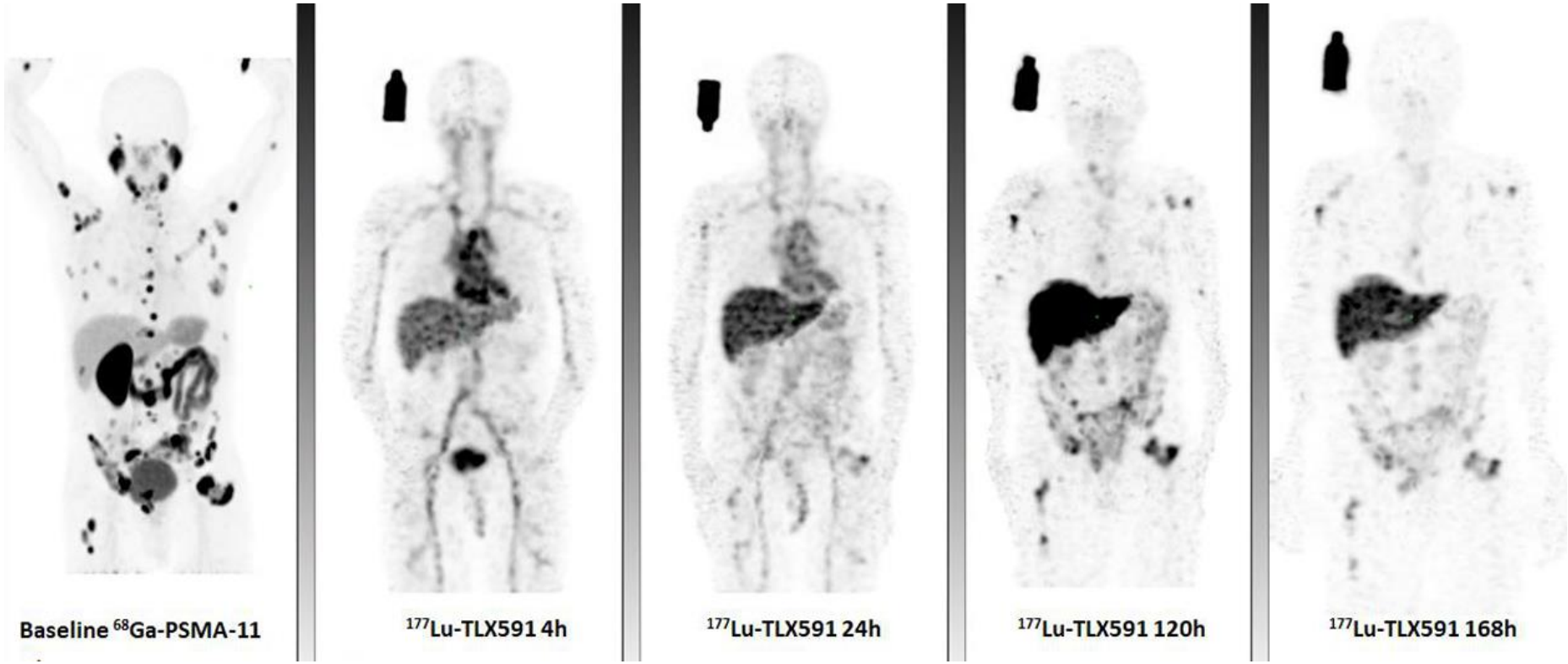


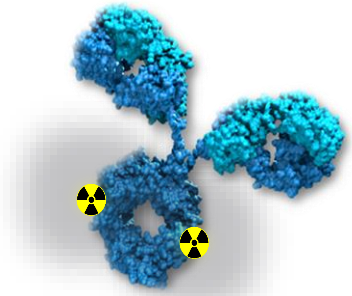
TLX591: Our Antibody based Prostate Cancer Therapy

Lu^{177} labelled with PSMA targeted full monoclonal antibody

Retained in the tumor up to 7 days post injection

Anticipated treatment regiment is two dose, 1 cycle.





Source: Lenzo, N, Meyrick, D, Hayward, C - 177Lu-DOTA-TLX591 Safety, Biodistribution and Dosimetry Study poster - presented at ASCO 2022

Telix is pioneering a new cancer modality

“See it, Treat it” is what we do

Glioblastoma

Ph	Name	Asset	Dx/Tx
I/II	IPAX-1	TLX101	Tx

Breast Cancer

Ph	Name	Asset	Dx/Tx
II	OPALESCENCE (IIT)	TLX250-CDx	Dx
I	Emory University (IIT)	TLX591-CDx	Dx

Lung and Ovarian Cancers

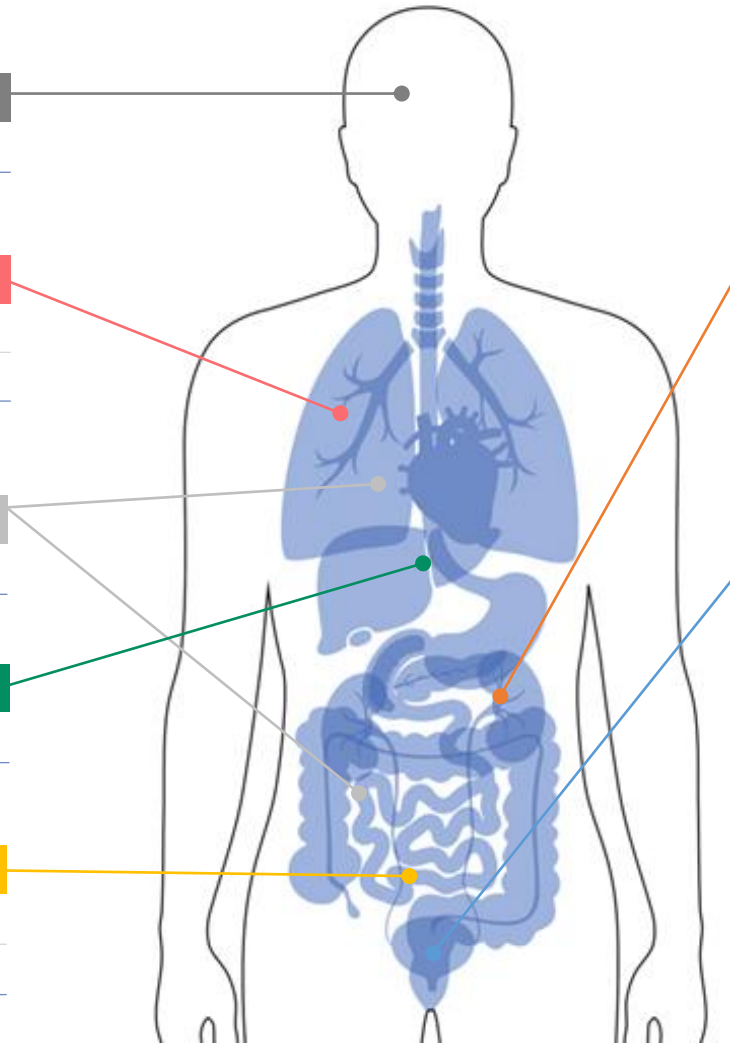
Ph	Name	Asset	Dx/Tx
I	Royal Adelaide (IIT)	APOMAB	Dx/Tx

Bone Marrow Conditioning

Ph	Name	Asset	Dx/Tx
I/IIa	TRALA (IIT)	TLX66	Tx

Bladder Cancer

Ph	Name	Asset	Dx/Tx
I	ZiP-UP (IIT)	TLX250-CDx	Dx
I	PERTINENCE (IIT)	TLX250-CDx	Dx



Kidney Cancer

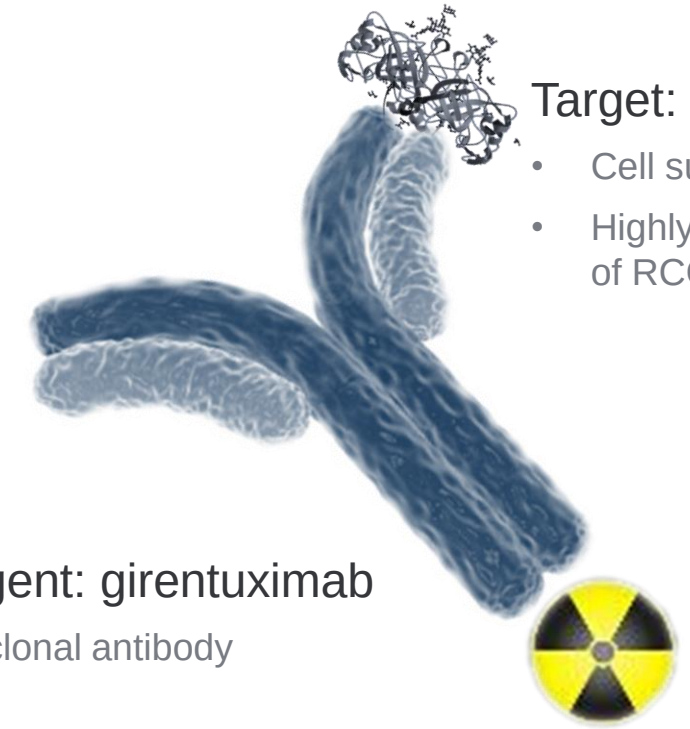
Ph	Name	Asset	Dx/Tx
III	ZIRCON	TLX250-CDx	Dx
I/II	ZIRDAC	TLX250-CDx	Dx
II	STARLITE-1 (IIT)	TLX250	Tx
II	STARLITE-2 (IIT)	TLX250	Tx

Prostate Cancer

Ph	Name	Asset	Dx/Tx
III	University of Linz (IIT)	TLX591-CDx	Dx
II	Emory University (IIT)	TLX591-CDx	Dx
II	ENHANCING (IIT)	TLX591-CDx	Dx
II	Mem. Sloan Kettering (IIT)	TLX591-CDx	Dx
N/A*	NOBLE	TLX599-CDx	Dx
III	PROSTACT	TLX591	Tx
I	CUPID	TLX592	Tx

*Registry study

^{89}Zr-TLX250 -(^{89}Zr-girentuximab) targets hypoxic nature of tumor



Target: CA-IX

- Cell surface antigen
- Highly expressed in >70% of RCC (esp. ccRCC)

Targeting Agent: girentuximab

- IgG1 monoclonal antibody

Payload: ^{89}Zr

- Positron emitter
- $T_{1/2}$ 3.3 days

Description:

- Antibody-based PET imaging agent targeting carbonic anhydrase 9 (CA-IX) for imaging of clear cell renal cell carcinoma (ccRCC)

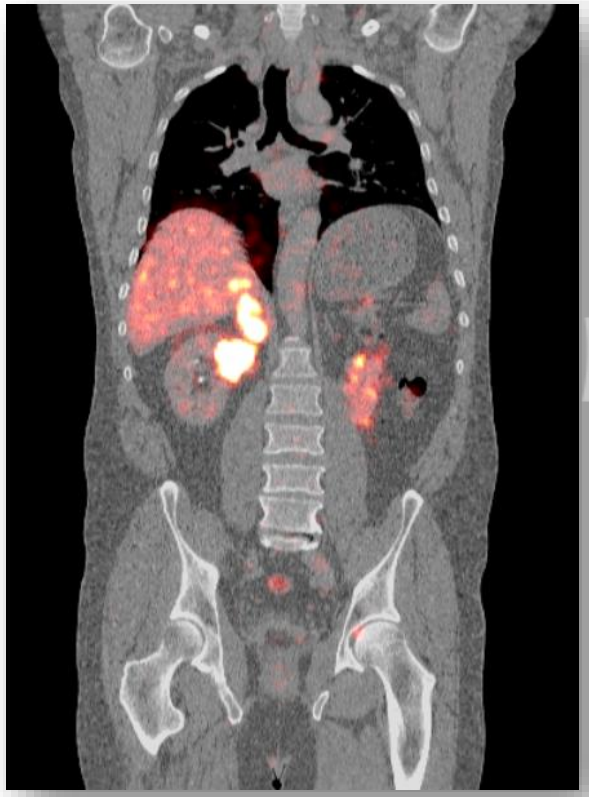
Clinical Status:

- ZIRCON Phase III (confirmatory/pivotal)

Unmet Need:

- ✓ Better / more cost-effective management of incidental findings
- ✓ Superior staging / re-staging
- ✓ Informing nephron-sparing surgery
- ✓ Rapid treatment response assessment

Future Directions



CDx

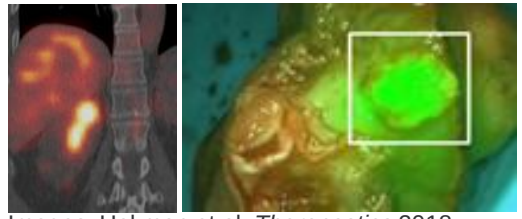
ZIRCON

- Other malignancies where CAIX might be beneficial for imaging over FDG PET/CT
- Colorectal, testicular, H&N
- Dosimetry for ^{177}Lu

OR

^{89}Zr-IR-girentuximab

- Dual-modality : Optical / PET



Images: Hekman et al. *Theranostics* 2018

Rx

^{177}Lu-DFO-girentuximab

STARLITE

- Combination I-O therapy studies
  - STARLITE1: TLX250 + pembrolizumab/axitinib in 1L ccRCC
  - STARLITE2: TLX250 + nivolumab in patients that have progressed on I-O therapy

For more information visit Illuccix.com

Thank you for your courage!