WARF THERAPEUTICS
Invest-Develop-Partner

Targeted Alpha Radiopharmaceutical for PMSA+ mCRPC

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Our goal: develop an actinium-based PSMA radiopharmaceutical for mCRPC with low salivary gland toxicity

- **WARF Therapeutics** is developing a radiopharmaceutical for the treatment of PSMA+ metastatic castration resistant prostate cancer
- Our molecule demonstrates **prolonged circulation, hepatic excretion, longer tumor retention,** and a **greater tumor uptake** vs. PSMA-617
- Our molecule will **utilize Actinium-225, an alpha emitter,** instead of Lutectium-177, a beta emitter
- PSMA / **Actinium-based radiopharmaceuticals show improved efficacy**, however they have a **high rate of salivary gland toxicity**
- We have designed our molecule to **improve the efficacy while eliminating the salivary gland toxicity**
- We are approximately **8 months away from filing an IND** for a microdose study that should prove our hypothesis
- We are seeking a partner that can continue the development and commercialize this radiopharmaceutical so that we can help the patients that need it the most

Partnering opportunity for PSMA targeting radiopharmaceutical

Program ART-101

Target: Prostate-specific membrane antigen (PSMA)

Primary indication: metastatic Castration-Resistant Prostate Cancer (mCRPC)

Modality: Small molecule radiolabeled with an alpha-emitter (Ac-225)

Development stage: Preclinical

Progress to date:

- Preclinical *in vitro* and *in vivo* data complete
- GMP production of the precursor is complete
- GLP toxicology is ongoing with an estimated completion in June

Development timing: 8 months to IND filing for a microdosing study

mCRPC is a large patient population with high unmet need

Large patient population

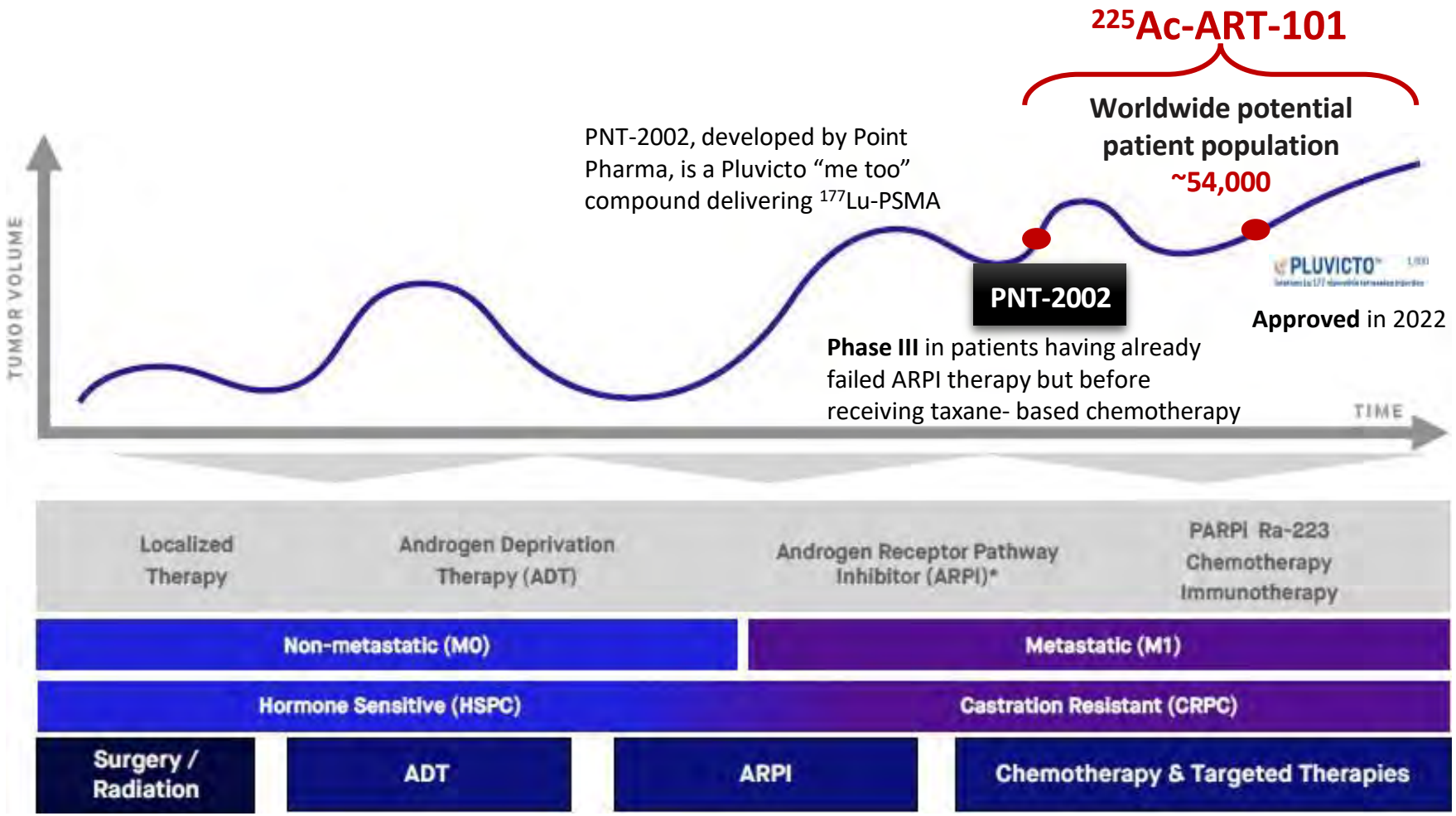
- PSMA is overexpressed in **~90%** of men with prostate cancer
- Worldwide patient population is **~54,000**
- Pluvicto is estimated to have **$2.6B** in worldwide sales in 2025

High unmet need

- **5-year relative survival** for patients classified as distant is only **34%**

Evaluate Pharma and SEER database

^{225}Ac-ART-101 could be positioned to treat patients that do not respond to Pluvicto and/or for subpopulations with diffuse metastasis



- Pluvicto' s worldwide sales are estimated to be **$2.6B** in 2025
- Its **response is close to 45%** meaning PSA decreases 50%+
- **25% only show partial** response
- **30% show no response** or do not qualify to receive the therapy
- **55% might be eligible** to receive an α-based radiotherapeutic

Source: EvaluatePharma

Treatable patient population = Incidence in US, EU and Japan of third-line treated patients x 90% with expression of PSMA

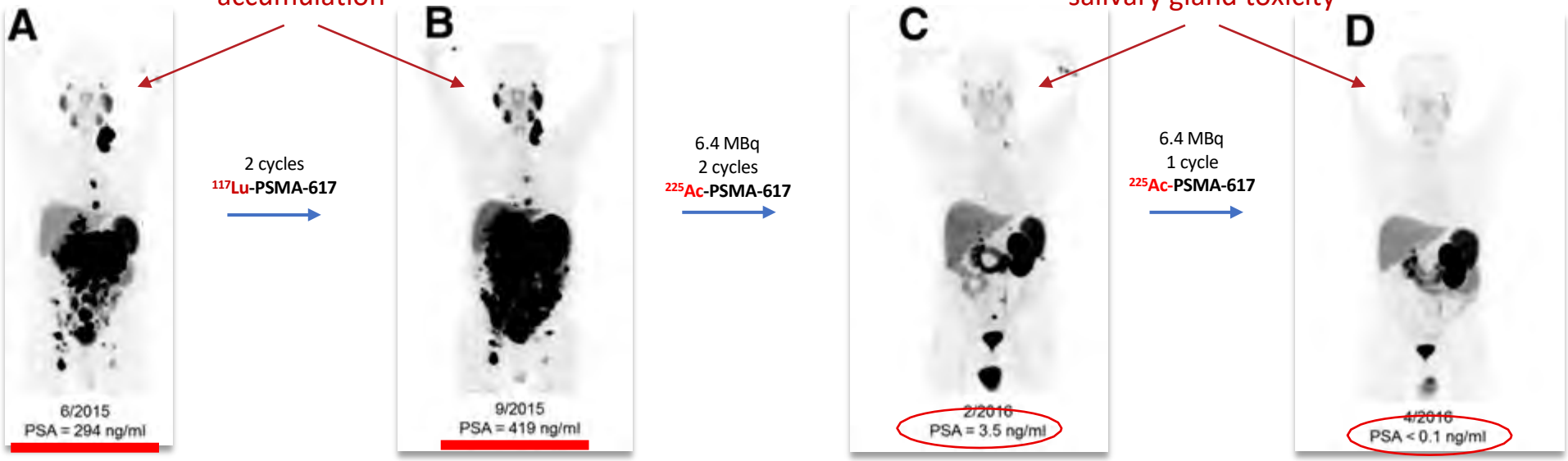
^{225}Ac-PSMA overcomes Pluvicto resistance

PSMA PET-CT scans of prostate cancer patient with peritoneal and liver infiltration

Patient
Radical prostatectomy
Radiotherapy of lymph node metastasis
Leuprorelin
Leuprorelin plus bicalutamide, 150 mg/d
Docetaxel (11 cycles)
Cabazitaxel (10 cycles)
Abiraterone
Enzalutamide (not tolerated)

Unspecific and enzyme-mediated accumulation

Radiation induced salivary gland toxicity



Initial PSA level was 294 ng/mL

After 2 cycles of ^{117}Lu-PSMA-617 the PSA level increased to 419 ng/mL and most lesions demonstrated tumor progression

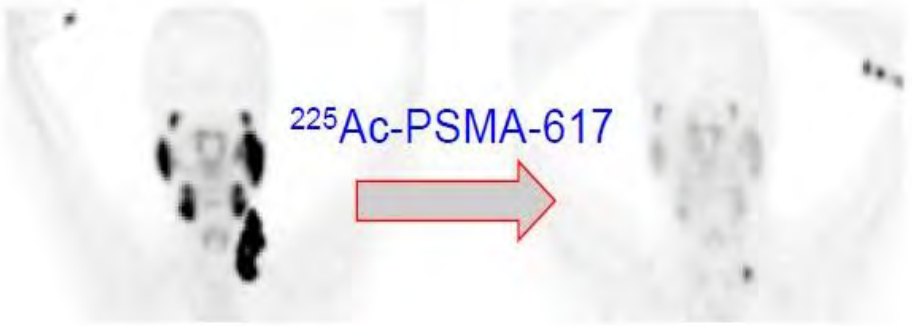
After 2 cycles of ^{225}Ac-PSMA-617 scans show a partial response

After 3 cycles ^{225}Ac-PSMA- 617 scans showed complete remission

Data extracted: THE JOURNAL OF NUCLEAR MEDICINE • Vol. 57 • No. 12 • December 2016

^{225}Ac-PSMA leads to xerostomia

- **Salivary gland toxicity is the dose-limiting side effect** for PSMA-targeted radionuclide therapy
- **68% experience xerostomia** after the **1st cycle** of treatment
- **100% experience xerostomia** after completing **4 to 5 cycles**
- **Xerostomia is reported in all ^{225}Ac studies**



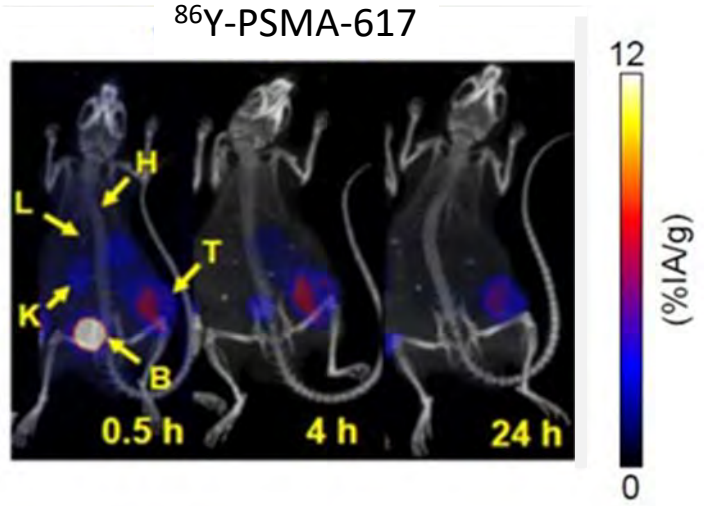
PSMA-TAT	n	Activity per Cycle	PSA Decline After TAT (Patients) ≤0%	PSA Decline After TAT (Patients) ≥50%	Median PFS/OS (Months)	Toxicity	References
^{213}Bi-PSMA-617	1	296 MBq		100% (1/1)	NA	NA	Sathekge et al., 2017 [105]
^{225}Ac-PSMA-617	2	100 kBq/kg		100% (2/2)	NA	Xerostomia	Kratochwil et al., 2016 [42]
	14	50–200 kBq/kg	22% (2/9)	44% (4/9)	NA/8.5	Xerostomia	Kratochwil et al., 2017 [106]
	40	100 kBq/kg	13% (5/40)	63% (24/38)	NA/>12	Xerostomia	Kratochwil et al., 2018 [107]
	1	8 MBq		100% (1/1)	NA	NA	Sathekge et al., 2019 [108]
	17	8–4 MBq	6% (1/17)	88% (15/17)	NA	Xerostomia	Sathekge et al., 2019 [109]
	1	8–6 MBq		100% (1/1)	NA	Xerostomia xero-phthalmia	De Medeiros et al., 2019 [110]
	73	8–4 MBq	18% (13/73)	70% (51/73)	15.2/18.0	NA	Sathekge et al., 2020 [111]
	26	8–4 MBq	11% (3/26)	65% (17/26)	3.5/7.7	Xerostomia, anemia, leucopenia, thrombope-nia	Feuerecker et al., 2020 [112]
	28	100 kBq/kg	18% (5/28)	39% (11/28)	12/17	Transient fatigue, xerostomia	Yadav et al., 2020 [113]
	2	NA	NA	NA	NA	Chronic kidney disease	Pelletier et al., 2021[114]
	13	8–6 MBq	15% (2/13)	69% (9/13)	NA/8.5	Xerostomia	Van der Doelen et al., 2020 [115]
^{225}Ac-PSMA I&T	1	8 MBq		100% (1/1)	NA	Xerostomia	Ilhan et al., 2020 [116]
	14	7.8 MBq	21% (3/14)	50% (7/14)	NA	Xerostomia	Zacherl etal, 2020 [117]

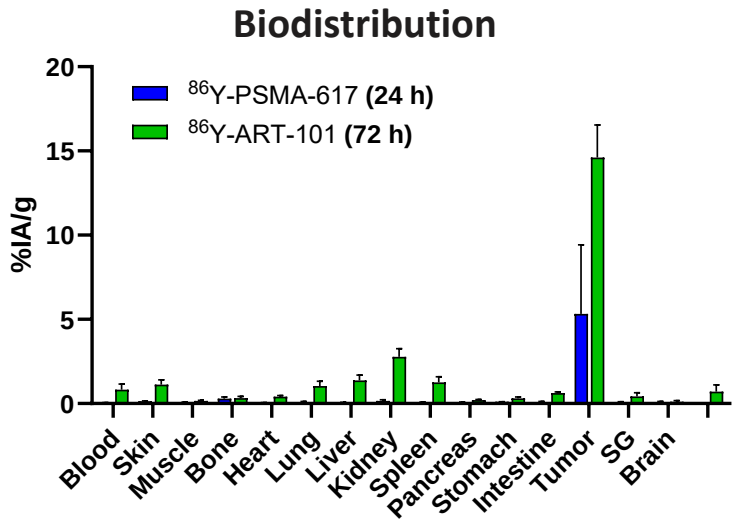
- Kratochwil et al. **J Nucl Med** 2018.
- Heynickx et al. **Nuc Med Bio,** 2021.
- Juzeniene et al. **Cancers,** 2021.
- Sathekge et al. **The Lancet Onc** 2023.

^{86}Y-ART-101 shows improved pharmacology vs. Pluvicto

PSMA-617

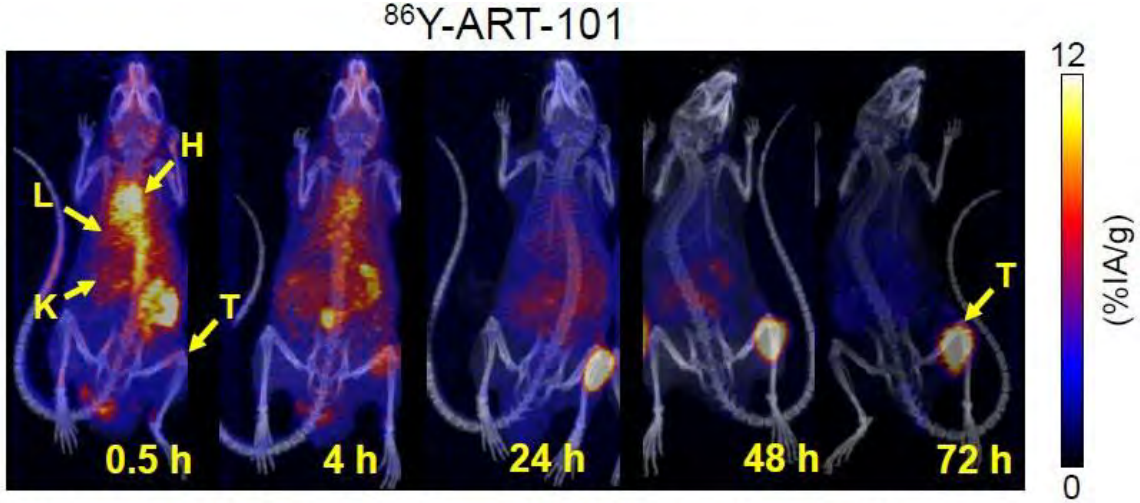
- Fast blood clearance (~1 hour)
- Low tumor uptake and poor retention
- Kidney clearance





ART-101

- **Prolonged blood circulation (~11 hours)**
- **Higher tumor uptake (3X) at 72 hours vs. PSMA-617 at 24 hours**
- **Tumor retention up to 72h**
- Predominant **hepatic** excretion



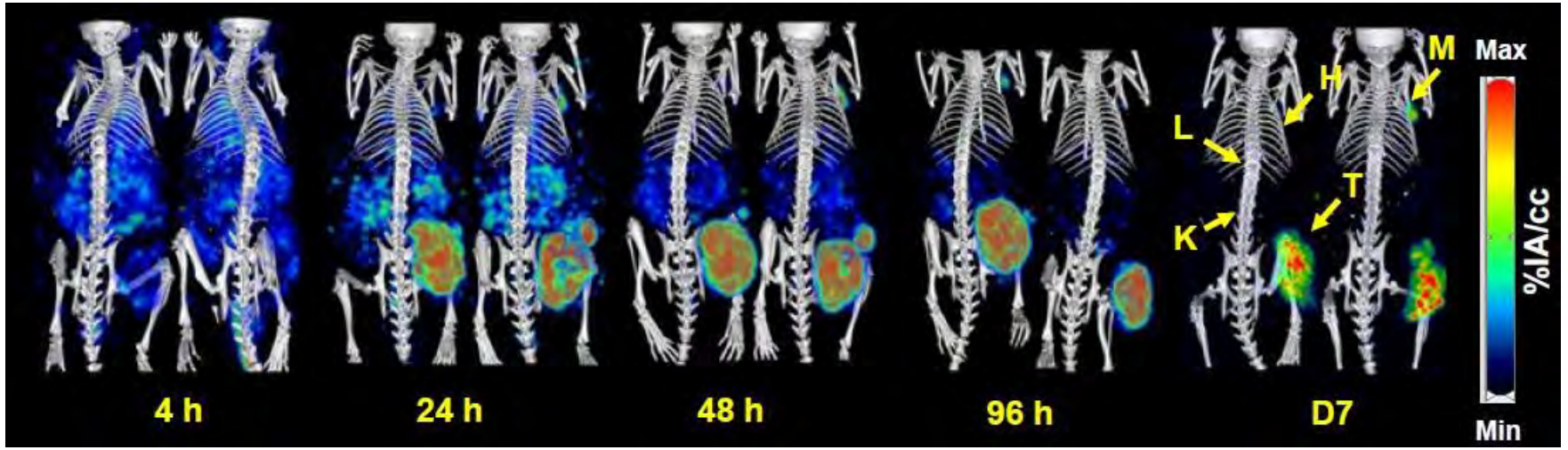
T: tumor; H: heart; L: liver; K: kidney; B: bladder

Unpublished data

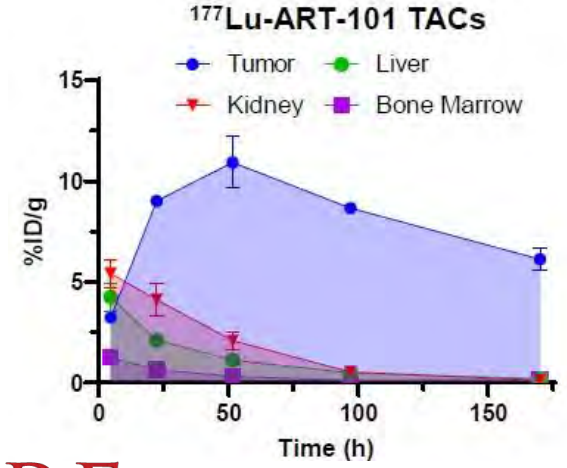
^{177}Lu-ART-101 is highly retained in Prostate Cancer (Pca) tumors

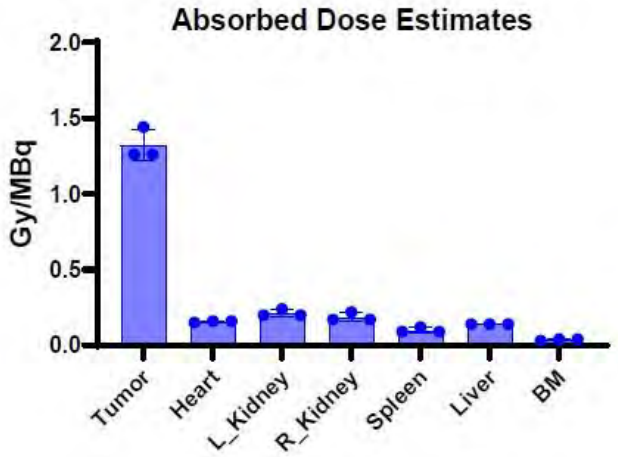
^{177}Lu-ART-101 longitudinal SPECT/CT

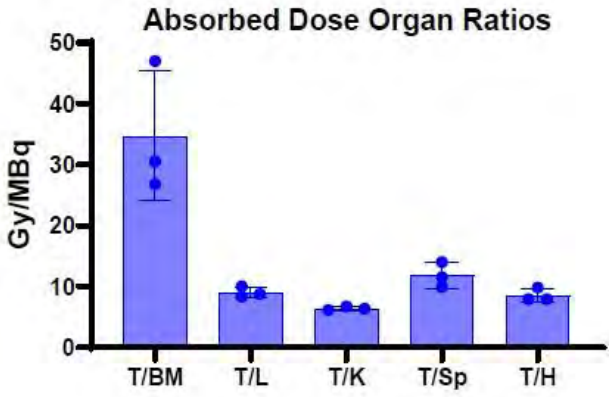
(2 mice shown)



H: Heart
L: Liver
K: Kidneys
T: Tumor
M: Metastases







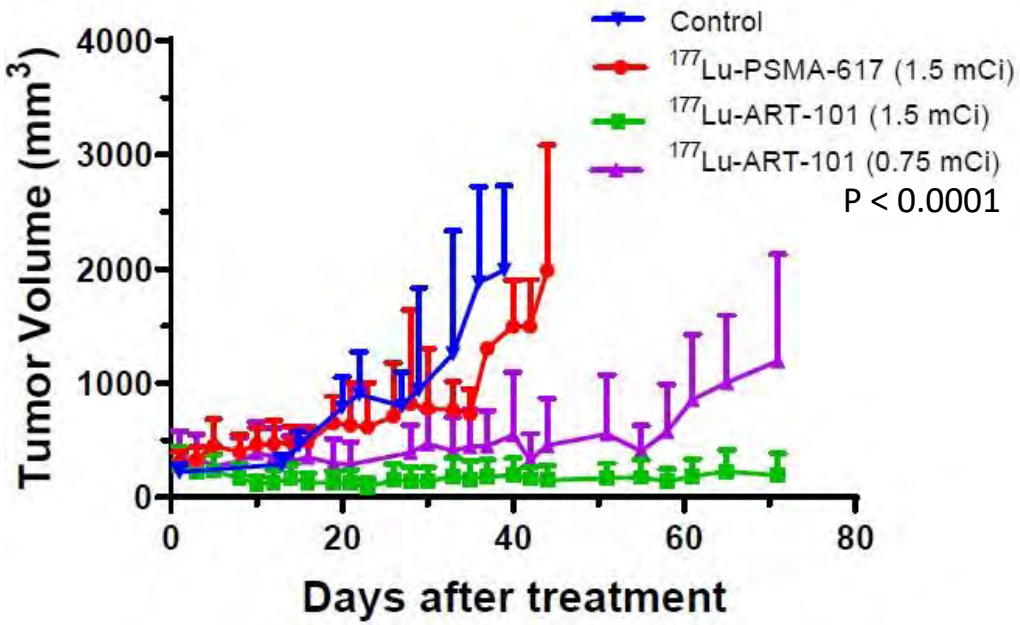
Unpublished data

^{177}Lu-ART-101 has greater tumor inhibition and overall survival vs. Pluvicto (^{177}Lu-PSMA-617)

Single Dose Study

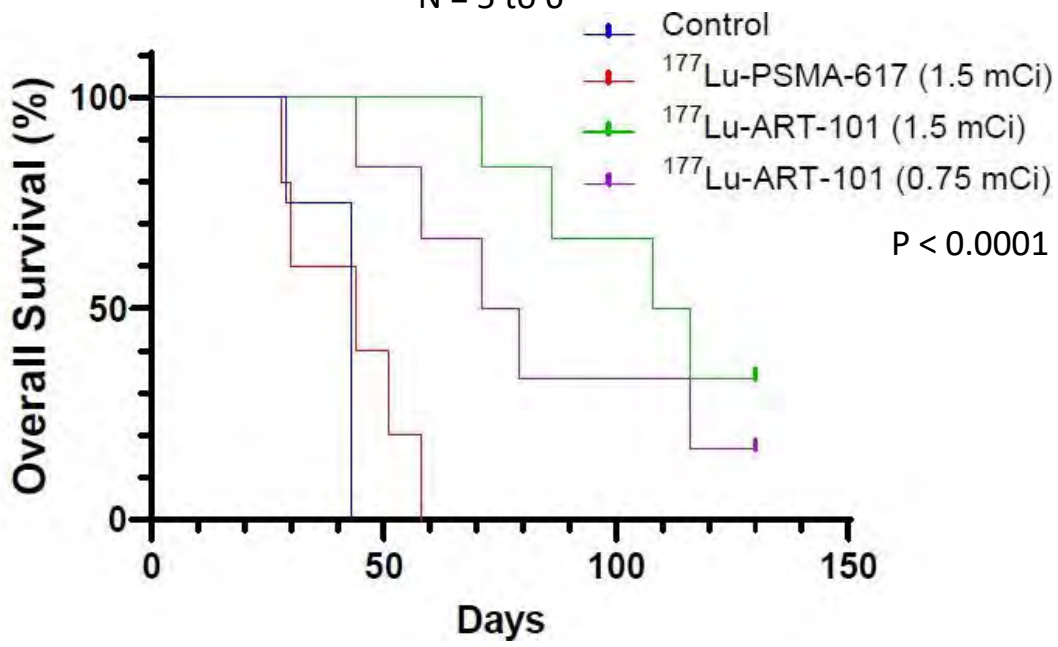
^{177}Lu-PSMA-ART-101 has greater tumor growth inhibition vs. Pluvicto

N = 5 to 6



^{177}Lu-PSMA-ART-101 has greater median overall survival vs. Pluvicto

N = 5 to 6



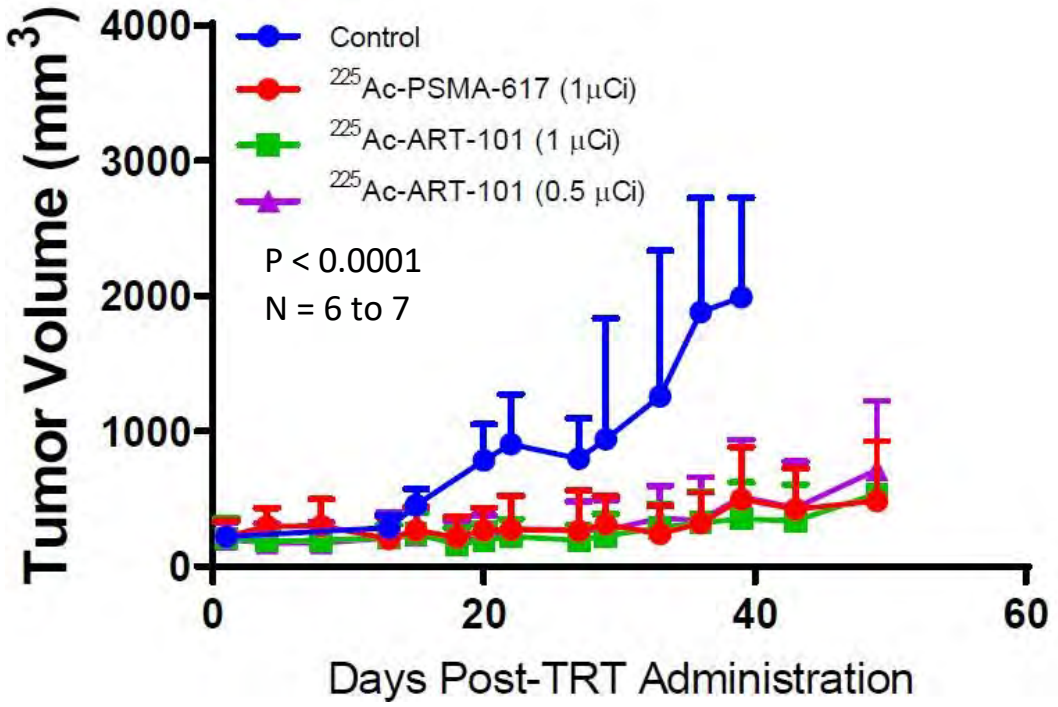
LNCaP tumor cell line in nude mice

Unpublished data

Actinium further extends survival with all molecules

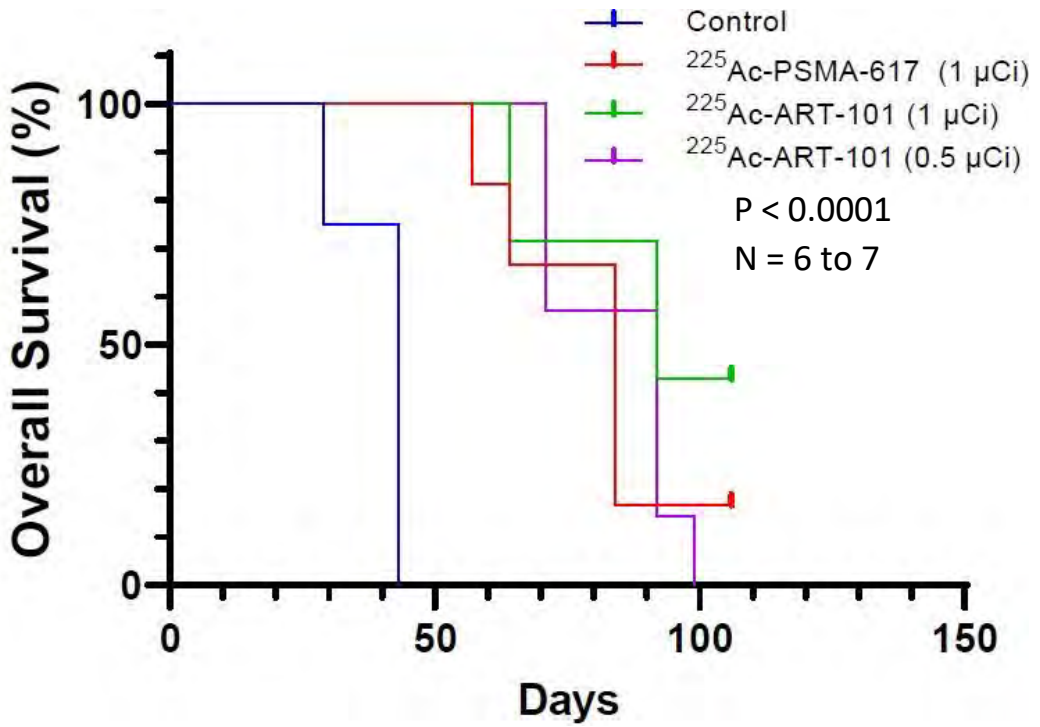
Single Dose Study

^{225}Ac-PSMA-ART-101 has similar tumor growth inhibition vs. ^{177}Ac-PSMA-617



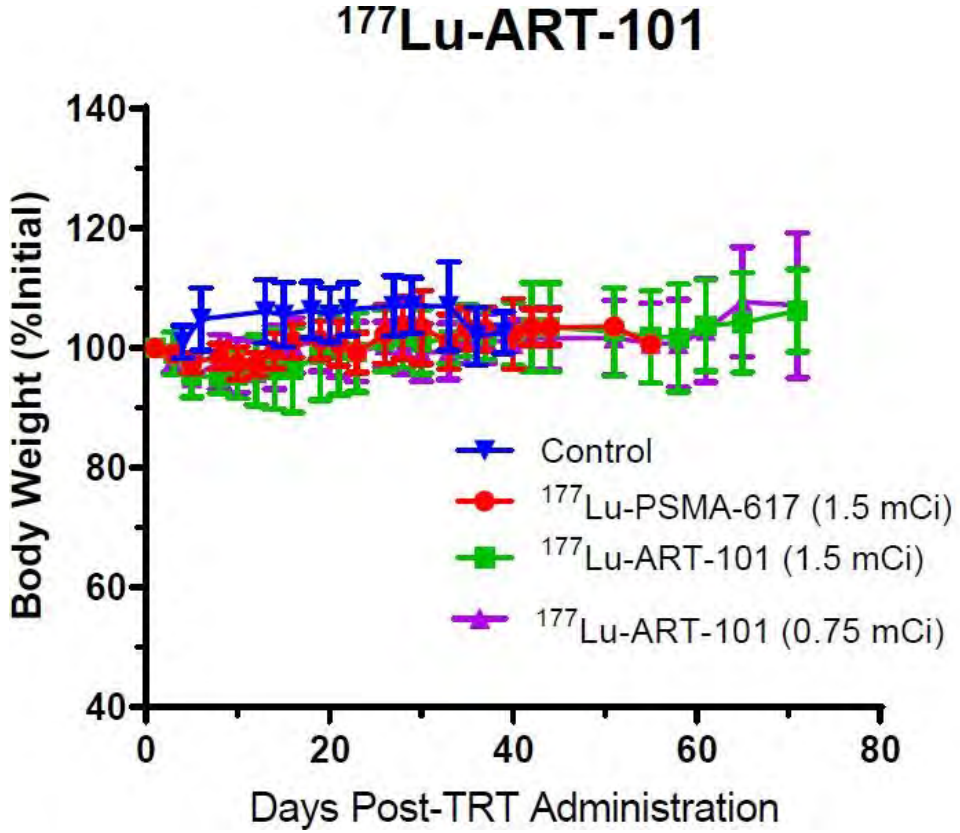
LNCaP tumor cell line in nude mice

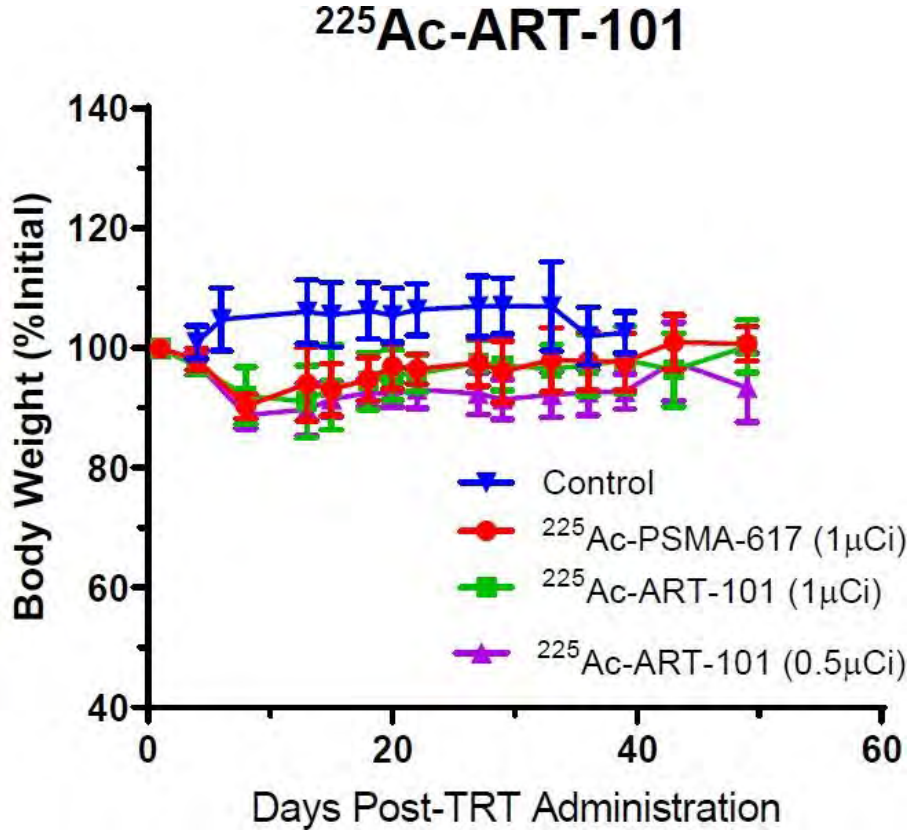
^{225}Ac-PSMA-ART-101 has greater median overall survival vs. ^{177}Ac-PSMA-617



Unpublished data

Mice body weights were unaffected by the treatments

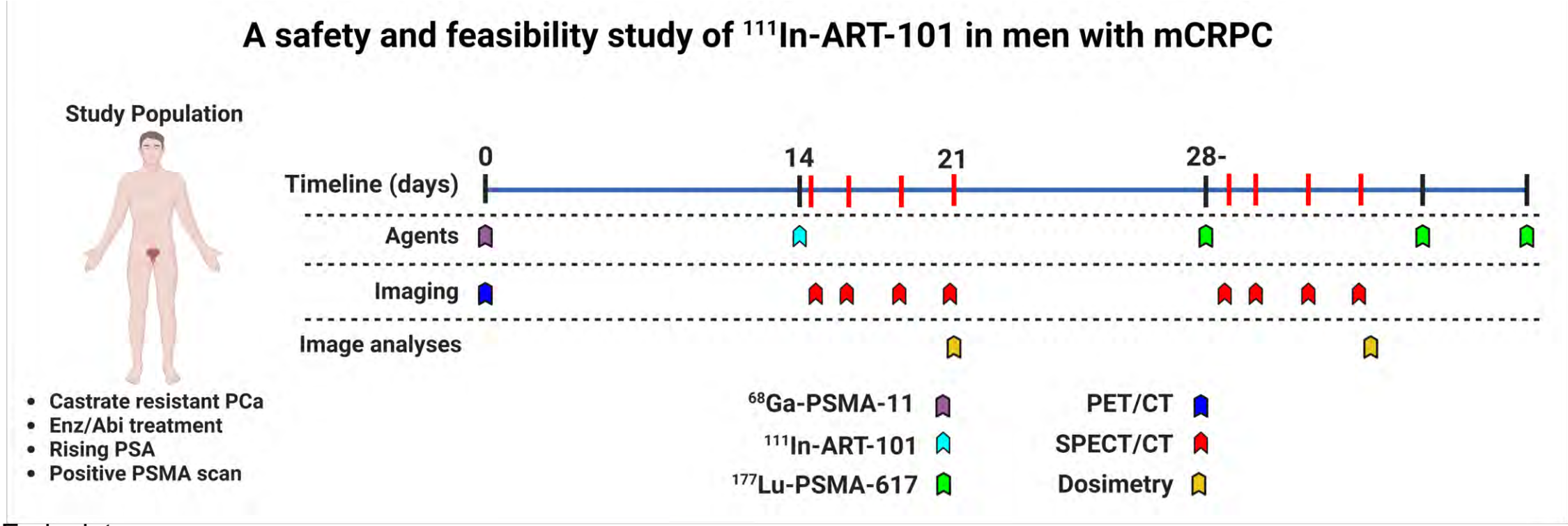




LNCaP tumor cell line in nude mice

Unpublished data

Microdose study will determine if ^{111}In-ART-101 spares the salivary gland



Endpoints:

1. The primary objective is to evaluate the safety and radiation dosimetry of ^{111}In-ART-101 when given by intravenous route.
2. We will evaluate the ability of ^{111}In-ART-101 to target and detect metastatic prostate cancer by visual qualitative and quantitative SUV analyses.
3. Compare ^{111}In-ART-101 tumor-to-organ uptake ratios and dosimetry estimates for ^{177}Lu/^{225}Ac-ART-101 with that of ^{177}Lu/^{225}Ac-PSMA-617.

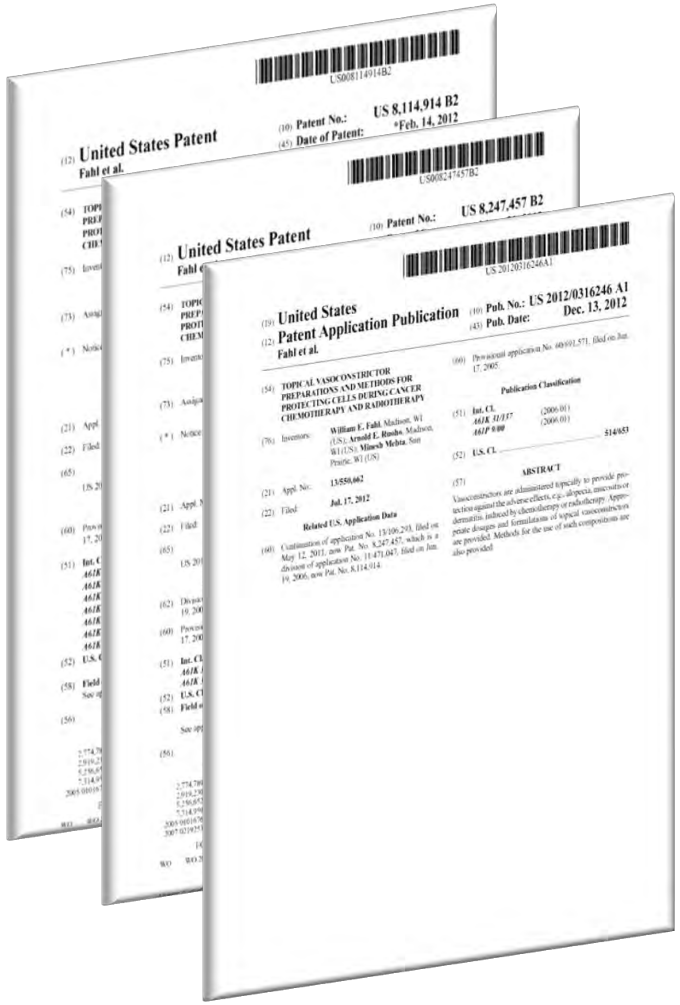
Intellectual property

US Provisional Application filed on 4/23/2021

PCT Application filed on 4/22/2022

- Composition of matter patent
- Patentability report received

US (expedited) application filing in progress



PSMA radiopharmaceutical opportunity

PSMA+ mCRPC is a large indication with high unmet need

ART-101 demonstrates

- prolonged circulation of ~ 11 hours
- tumor retention up to 72 hours
- 3x greater tumor uptake @ 72 hours vs. PSMA-617 @ 24 hours
- Hepatic excretion
- Utilizes Actinium which shows superior overall survival compared to Lutetium

IND for microdosing study will be compete in ~8 months

Microdosing study will show if ^{111}In-ART-101 spares the salivary glands

WARF is seeking a partner to continue the development and commercialize this asset

- Worldwide, exclusive rights are available
- We are open to various deal structures such as licensing, co-development, build to buy or startup formation

For more information contact John Nagel at jnagel@warf.org