Longitudinal Analysis of Cell-Free RNA in Patients with Metastatic Prostate Cancer Undergoing 177Lu PSMA-617 Therapy: Elucidating Mechanisms of Resistance and Formulating Optimal Treatment Strategies

11/6/2024

Colin Bergstrom, MD

Stanford MEDICINE | School of Medicine

Disclosures:

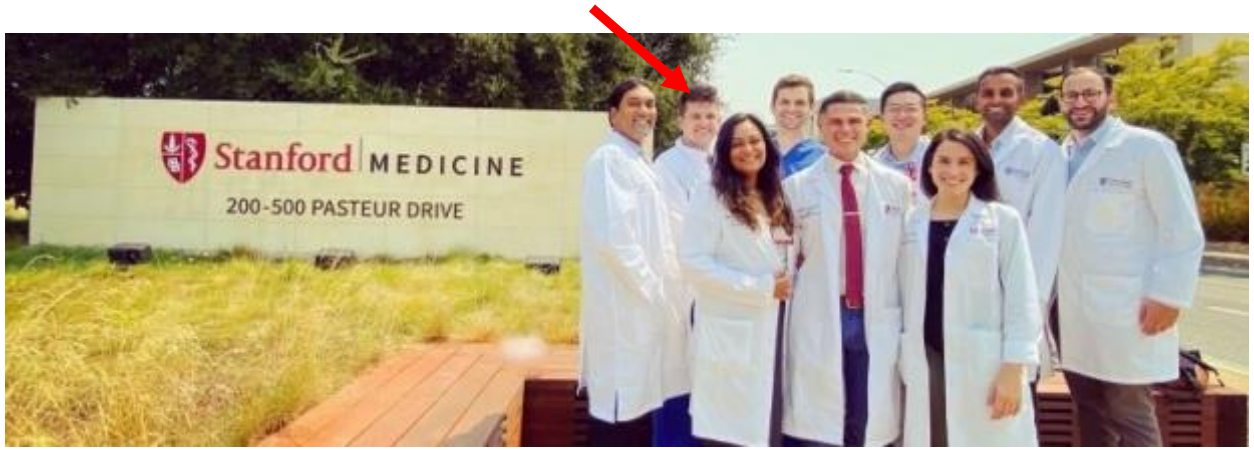
My Path

UNIVERSITY OF OREGON

OREGON HEALTH & SCIENCE UNIVERSITY

My Path Continued

UT Southwestern
Medical Center



Metastatic Prostate Cancer Overview

• Prostate cancer is the most common cancer among men in developed countries and the second most common cause of cancer-related death in men in the United States.

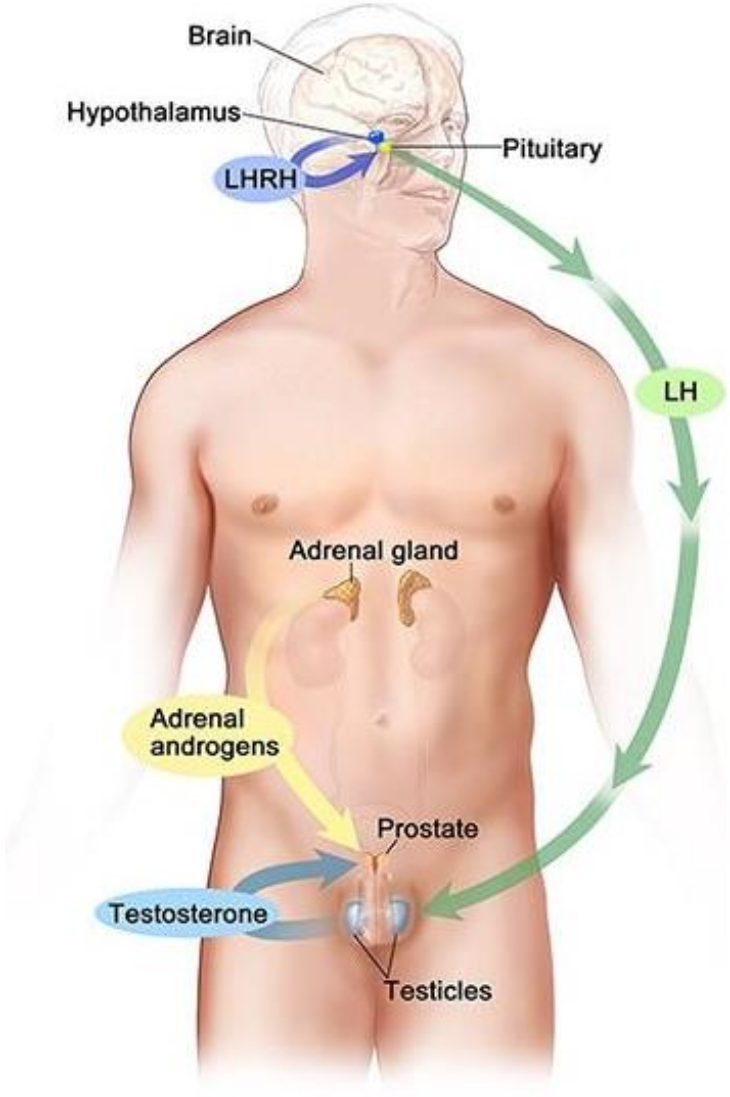
• A substantial number of prostate cancer patients continue with disease progression and metastatic spread despite androgen deprivation therapy (ADT), leading to metastatic castration-resistant prostate cancer (mCRPC), the disease's most serious form.

• mCRPC remains incurable and fatal with an expected median survival of only 2-3 years, despite the availability of multiple classes of therapy.

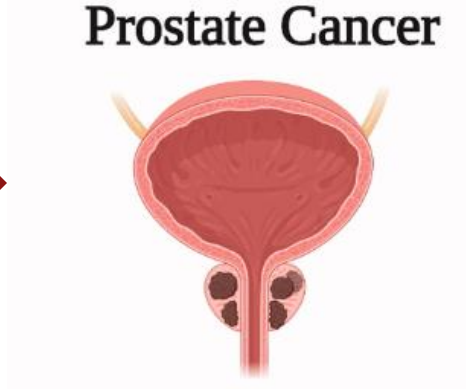
Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7–30.

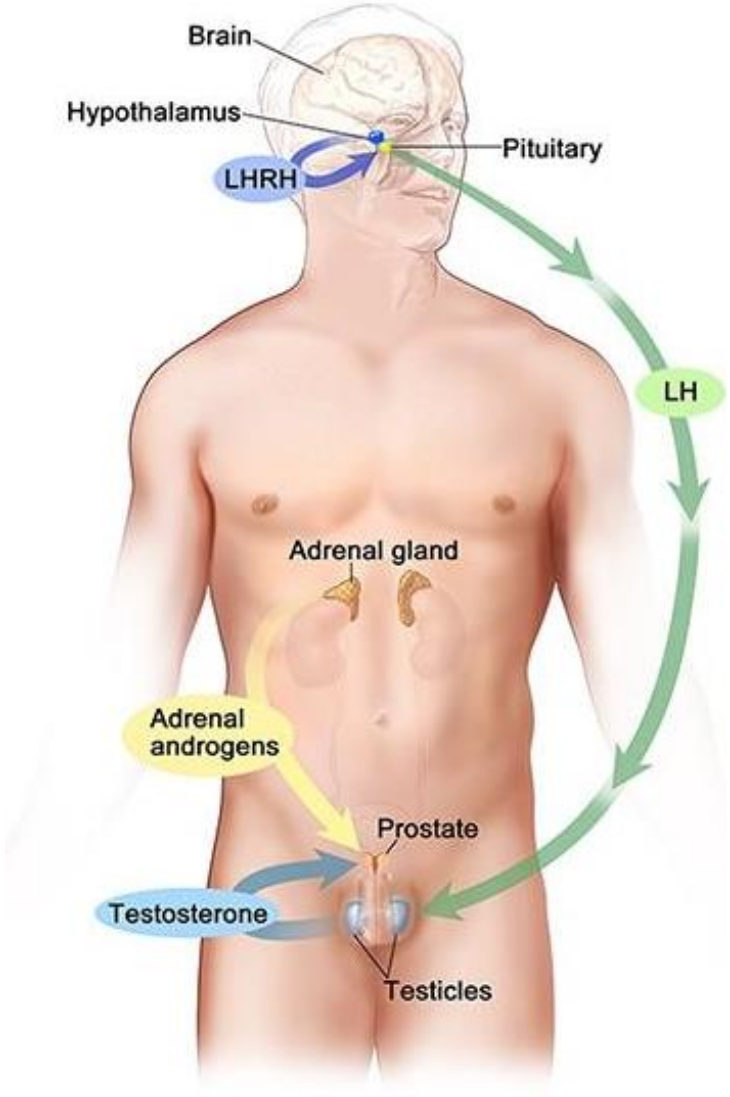
Metastatic Prostate Cancer Treatment Paradigm Simplified



Androgens



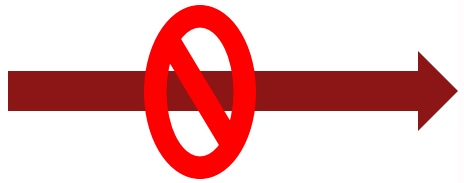
Metastatic Prostate Cancer Treatment Paradigm Simplified



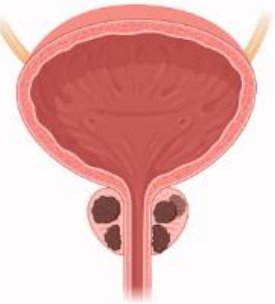
Androgen Deprivation Therapy

Testosterone < 50 ng/dl

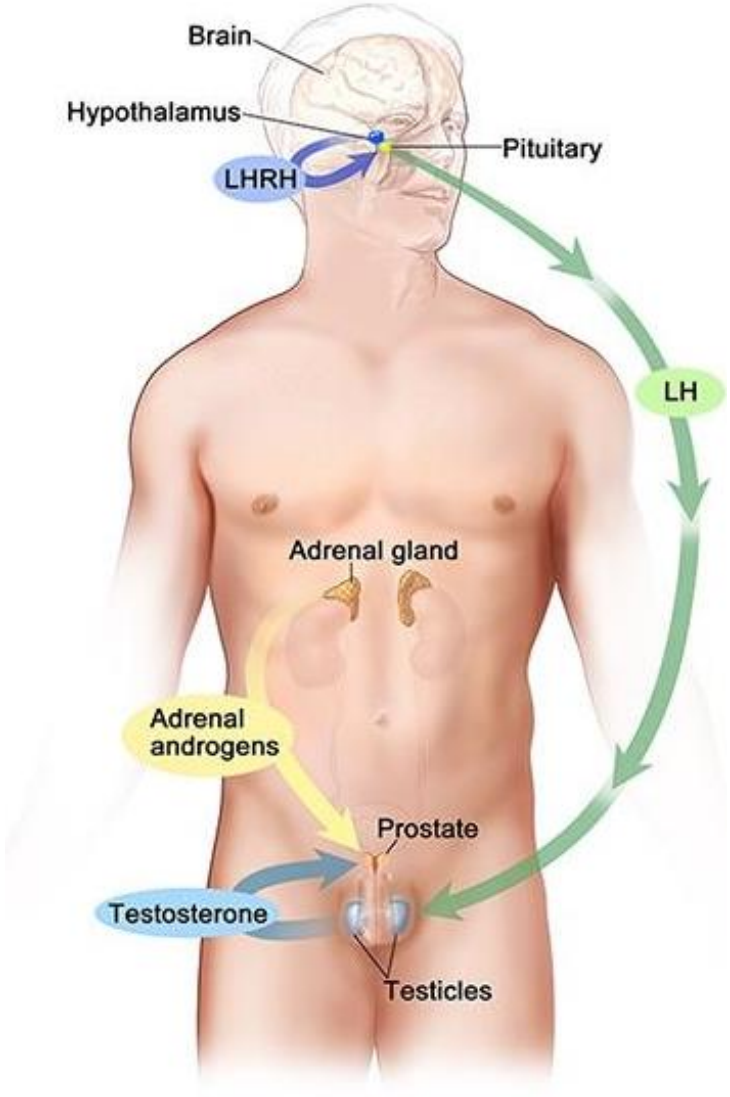
Androgens



Prostate Cancer



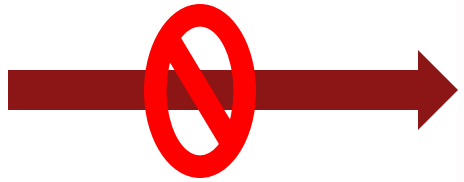
Metastatic Prostate Cancer Treatment Paradigm Simplified



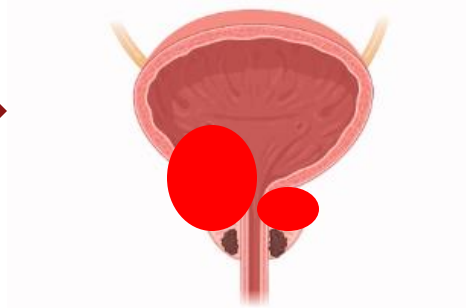
Androgens

Androgen Deprivation Therapy

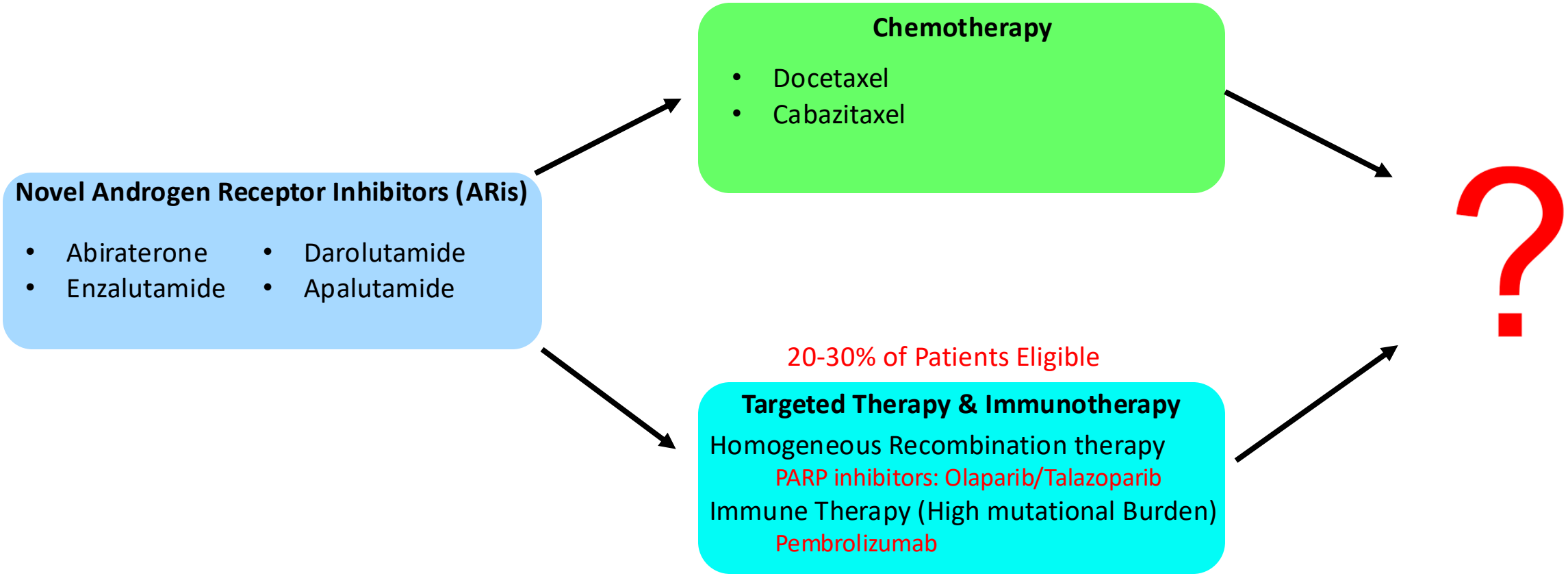
Testosterone < 50 ng/dl



"Castrate Resistant Prostate Cancer"



Metastatic Prostate Cancer Treatment Paradigm Simplified



VISION Trial

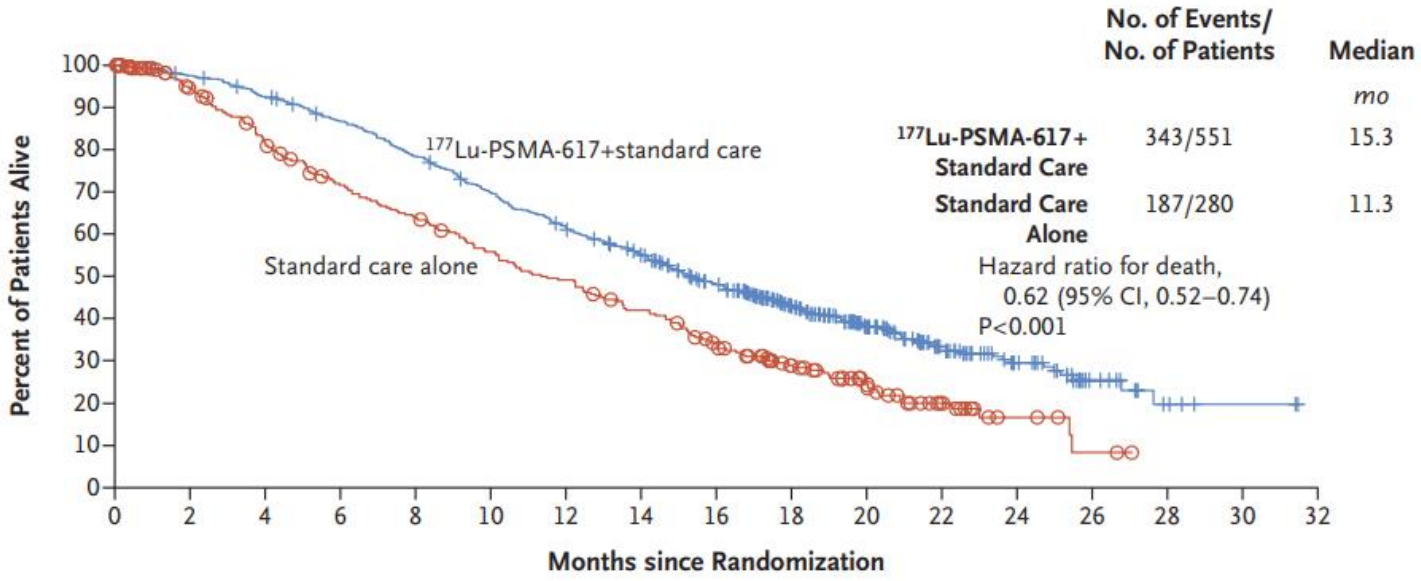
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

Overall Survival



- Patients received: Taxane and Androgen Receptor Pathway Inhibitor
- Improved progression free survival (HR 0.40)
- Improved Overall Survival (15.3 vs 11.3 months, HR 0.62)
- Well tolerated

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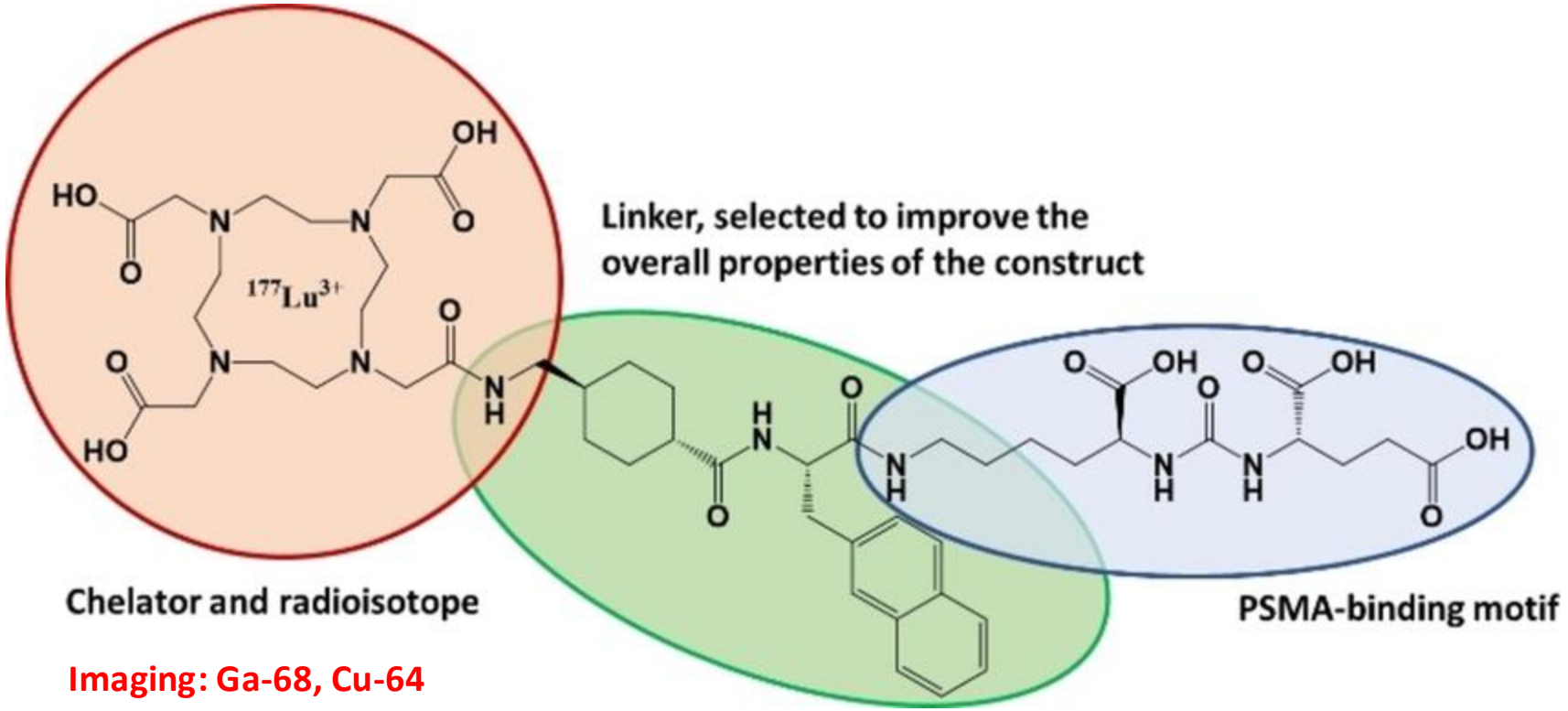
Sartor NEJM 2021

Pluvicto (Lutetium Lu 177 Vipivotide Tetraxetan) approval (ie 177Lu-PSMA-617)

On March 23, 2022: “the FDA approved Pluvicto (active ingredient lutetium Lu 177 vipivotide tetraxetan) for the treatment of adult patients with prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.”

Theragnostics



Imaging: Ga-68, Cu-64

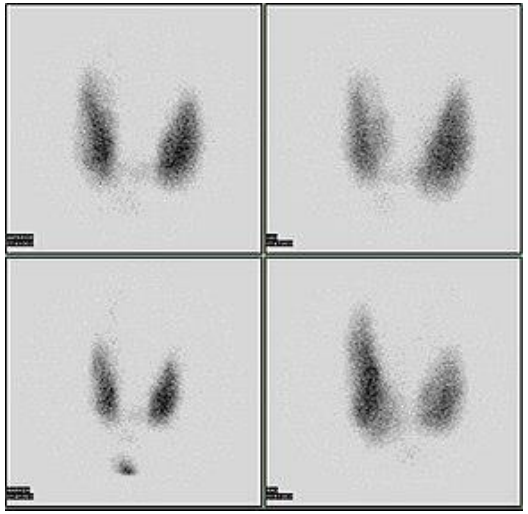
Therapy: Lu-177, Ac-225

EFMC: Trends in Medicinal Chemistry and Chemical Biology. Chembiochem. 2023;24(7):e202200690.

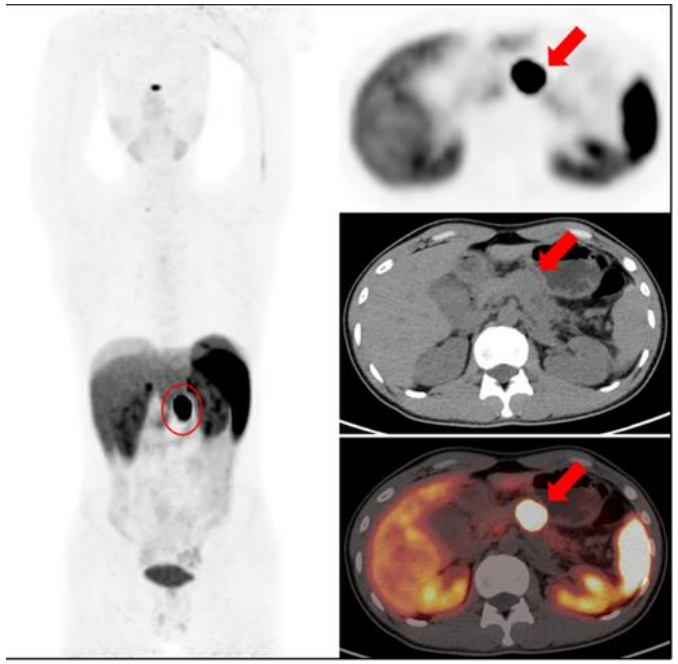
Theragnostics

Other Examples:

Thyroid Cancer: Radioactive Iodine

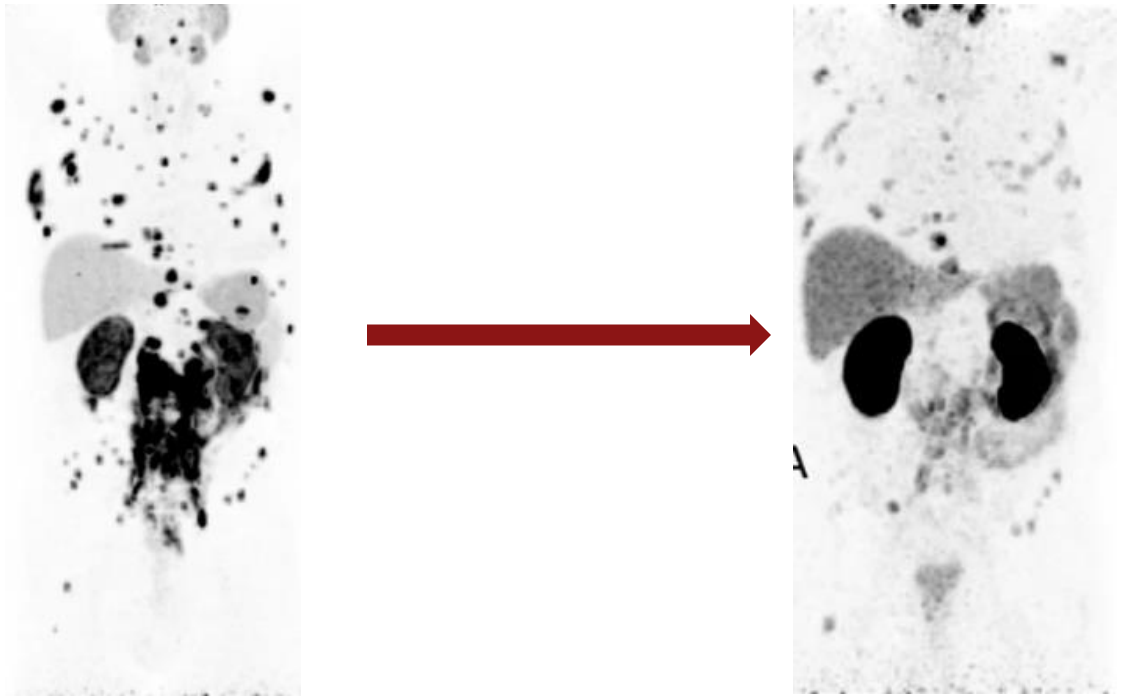


Neuroendocrine tumors:Lu-177-DOTATATE



Endocrine 83.2 (2024): 502-510.

Patient Perspective



"Before my first treatment, even sitting up in bed was difficult, and standing on my own was nearly impossible. But with Pluvicto, I've gotten a part of my life back. It's helped me regain my independence without the harsh side effects I experienced with chemotherapy."

Pluvicto (Lutetium Lu 177 Vipivotide Tetraxetan)

- Given for every 6 weeks for a total of 6 cycles in patients with PSMSA positive disease
- Response rate: 30% radiographic, with ~ 6% who had a Complete Response
- 46% patient had a PSA decrease greater than 50%
- Progressive Free survival: ~9 months
- Overall Survival: 15.3 months
- At Stanford: ~160 patients thus far have been treated

Future Developments in Prostate Theragnostics

- New Prostate Theragnostics
  - Examples: 177Lu-PNT2002 (Lantheus and POINT Biopharma_
  - Results presented at ESMO 2024 showing similar efficacy to Pluvcito

- Given earlier in treatment course (ie chemotherapy naïve)
  - PMSAfore trial: Published Lancet 2024

- Given in combination with other therapies (ie immunotherapy)
  - Lancet Oncol. 2023 Nov;24(11):1266-1276.

Biomarkers in Prostate Cancer

- Goal: Assist in treatment selection, modification (continuation vs discontinuation)

- Current Biomarkers:
  - **Prostate Specific Antigen (PSA):**
  - Do not entirely reflect course of disease
  - Example: PSA correlation to clinical outcomes such as OS (TheraP trial)
  - Other Examples: Different rates of decline or time to nadir, discordance to new visceral sites
  - **PET/CT and Other imaging modalities**
  - Frequency, availability, osseus and other visceral metastases

Seminars and Original Investigations 29, 593–601 (2011).
Eur. Urol. 65, 270–273 (2014).

European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:2784–2793
https://doi.org/10.1007/s00259-024-06718-6

ORIGINAL ARTICLE

Same-day post-therapy imaging with a new generation whole-body digital SPECT/CT in assessing treatment response to [^{177}Lu]Lu-PSMA-617 in metastatic castration-resistant prostate cancer

Hong Song[1] · Maria Isabel Leonio[1] · Valentina Ferri[1] · Heying Duan[1] · Carina Mari Aparici[1] · Guido Davidzon[1] · Benjamin L. Franc[1] · Farshad Moradi[1] · Jagruti Shah[1] · Colin P. Bergstrom[2] · Alice C. Fan[2] · Sumit Shah[2] · Ali Raza Khaki[2] · Sandy Srinivas[2] · Andrei Iagaru[1]

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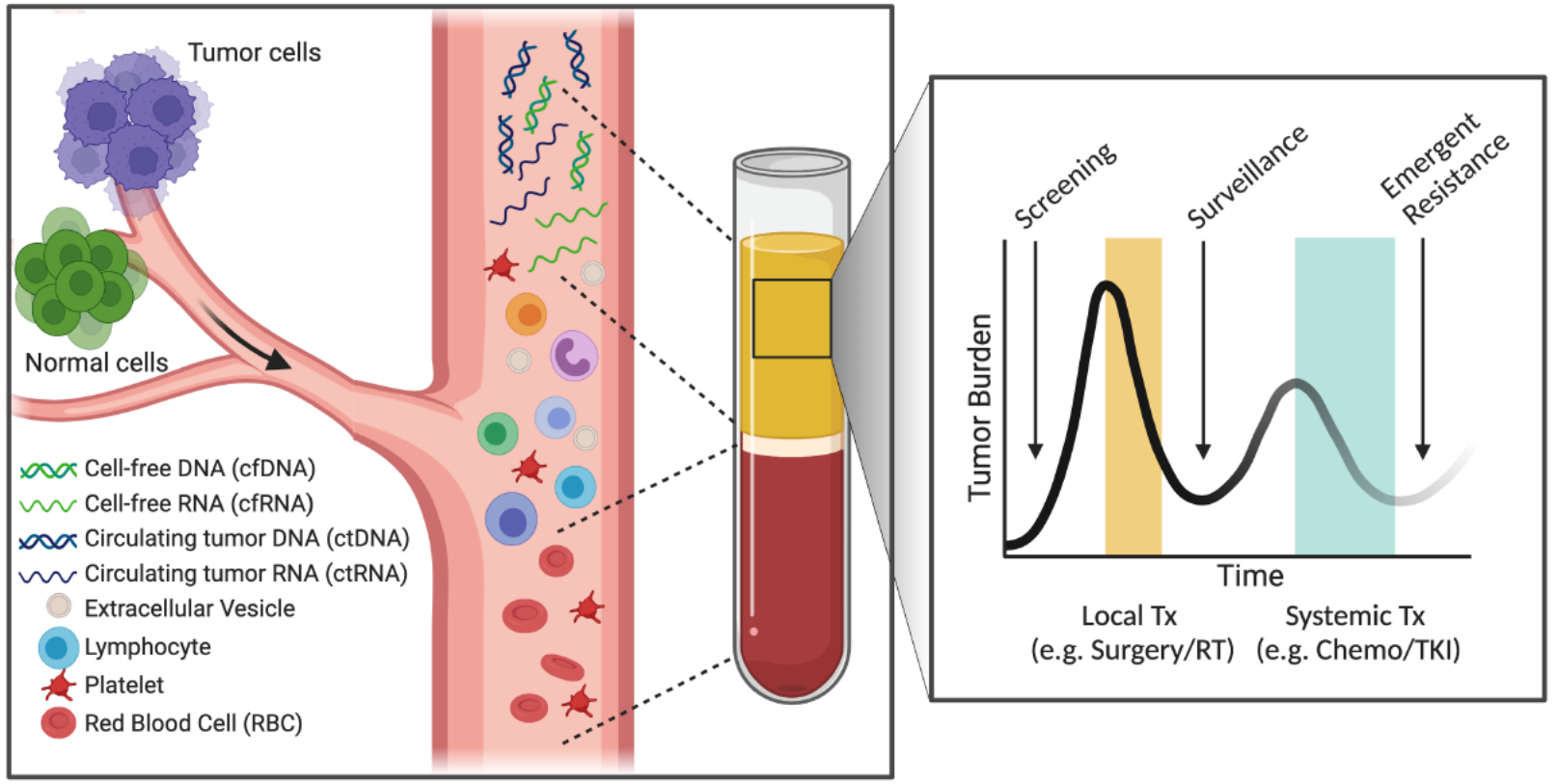
Biomarker in Prostate Cancer: Cell-free Nucleic Acids

Emerging Areas

- Screening
- Diagnostics
- Adjuvant Treatment Selection
- Surveillance



Circulating Free DNA

Advantages:

- Readily accessible and low risk to obtain
- Captures Heterogeneity of tumor and tumor sites

Limitations:

- Variations in tumors in shedding DNA
- Lower sensitivity depending on tumor burden
- Difficulty capturing genetic modifications that alter RNA expression: alternative splicing, stability, and allele-specific methylation.

Circulating Free DNA

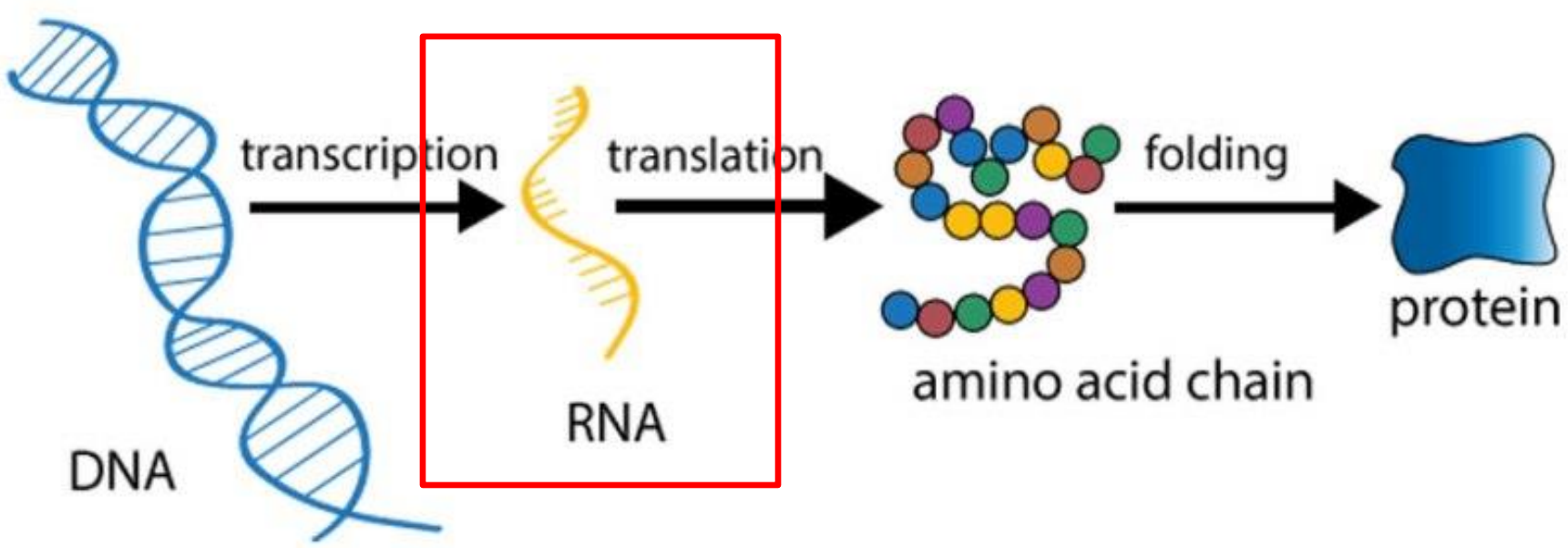
Mixed Results:

- Annals of Oncology, Volume 35, S975 - S976 September 2024
  - 37 Patients, lower ctDNA after 2 cycles correlated with improved response

- Cancer Res (2023) 83 (7_Supplement): 5614.
  - Certain mutations (ie AR or PTEN) correlated with worse PSA response, but levels not significantly correlated with clinical outcomes

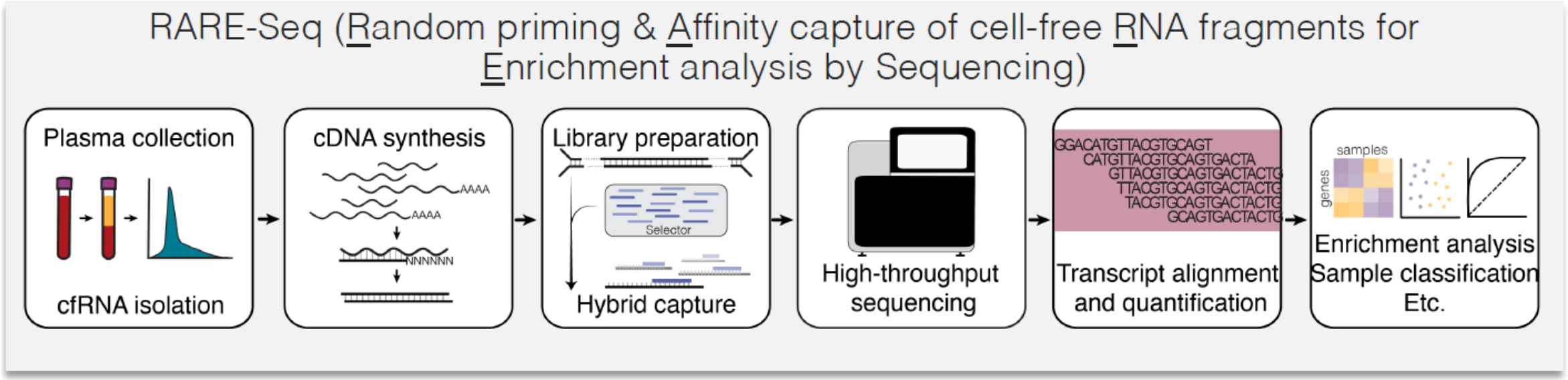
- Journal of Nuclear Medicine November 2023, 64 (11) 1721-1725
  - Frequency of mutations not correlated to outcomes

Cell-Free RNA



- Reflects post-transcriptional modifications such as splicing, polyadenylation
- High concentration and signal strength compared to ctDNA (up to 50x greater)
- Has potential to offer real-time assessment of tumor evolution and response

Research Methodology: RARE-Seq



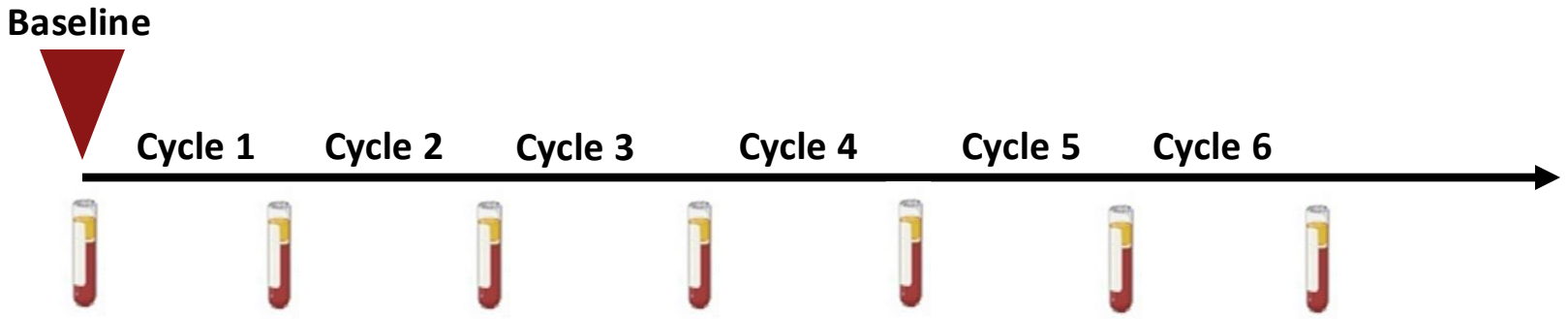
Courtesy of Deihn Laboratory

Project Aims

Aim 1: To evaluate the predictive utility of circulating tumor RNA (ctRNA) in patients with metastatic castration-resistant prostate cancer (mCRPC) at baseline or prior to initial therapy with Lutetium-177-PSMA-617 for treatment response, time to next treatment and progression-free survival.

Aim 2: To determine whether dynamic temporal changes in ctRNA levels in real time correlate with, or anticipate treatment responses in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving ^{177}Lu.

Research Methodology: Analytics/Sampling



Research Progress

- Started enrolling patients June 2024

- Total Enrollment: N=25 patients

- Cycles Completed
  - 1 cycles: 9 patients
  - 2 cycles: 9 patients
  - 3 cycles: 2 patients
  - 4 cycles: 5 patients

- Treatment Status:
  - 23 patients still undergoing treatment
  - 2 patients completed therapy due to progression

Acknowledgements

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- Stanford Nuclear Medicine and Theragnostic Program

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- Maximilian Diehn, M.D, PhD
- Andrei Iagaru, M.D.

Thank you!