3rd Annual Southern California Genitourinary Cancer Research Forum

Panel: Prostate Studies (Localized, Salvage/BCR, mHSPC, mCRPC)

Moderator: Tanya Barauskas Dorff, MD

Speakers:

Arash Rezazadeh, MD

Amar U. Kishan, MD

John Shin, MD

David J. Benjamin, MD

Przemyslaw Twardowski, MD

Alex Chehrazi-Raffle, MD

Disclosures

Tanya Barauskas Dorff, MD
Professor and Vice Chair for Clinical Affairs
Department of Medical Oncology and Therapeutics Research Leader
Developmental Cancer Therapeutics Program
City of Hope

- *Consultant for Abbvie, Bayer, BlueEarth, Janssen, Johnson and Johnson, Novartis, and Pfizer; Research/Grant Support from Amgen, AstraZeneca, and Dendreon.*

Arash Rezazadeh MD
GU Medical Oncologist
University of California Irvine

- *Consultant for AimedBio, Amgen, AstraZeneca, AVEO Oncology, Bayer, Bicycle Therapeutics, Bristol-Myers Squibb, Eisai, EMD Serono, Exelixis, Gilead Sciences, Janssen, Myovant Sciences, Pfizer, Sanofi, Sumitomo Pharma Oncology; On the Speaker's Bureau for Amgen, AVEO Oncology, Bayer, Bristol-Myers Squibb, Eisai, EMD Serono, Exelixis, Gilead Sciences, Janssen, Myovant Sciences, Pfizer, and Sanofi; Grant/Research Support from Amgen, Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Eikon Therapeutics, Exelixis, Genentech, Immunomedics, Janssen, Merck, Mirati, Navir, Novartis, POINT Biopharma, and Seattle Genetics.*

Amar U. Kishan, MD
Professor, Executive Vice Chair
University of California, Los Angeles

- *Consultant for Lantheus and Novartis; Grant/Research Support from Artera, Lantheus, Novartis, and ViewRay Systems; Stock/Shareholder for MiraDx.*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of AMG509 (xaluritamig), PSCA CAR T, STEAP2 CAR T, pasritamig, luxdegalutamide, abbv-969, CEA immunocytokine, Ac225-CEA, Ac225-PSMA, INV-9956 (as part of phase I trial at Hoag), and JANX007 (as part of phase I trial at Hoag)

Disclosures

John Shin, MD
Assistant Professor, Division of Medical Oncology/Hematology
Loma Linda University Health

- *No relevant financial relationships with any ineligible companies.*

David J. Benjamin, MD
Medical Oncologist
Hoag Family Cancer Institute

- *Consultant for AIMED BIO, Astellas, AVEO Oncology, Bayer, Dendreon, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, Janssen, Janux, Merck KGAA and Seagen; On the Speakers Bureau for Merck Sharpe Dohme.*

Przemyslaw Twardowski, MD
Professor of Medical Oncology and Urologic Oncology
Department of Urologic Oncology
Saint John's Cancer Center
Providence Saint John's Health Center

- *On the Speakers Bureau for Astellas, Bayer, Johnson & Johnson, and Pfizer.*

Alex Chehrazi-Raffle, MD
Assistant Professor, Division of Medical Oncology & Experimental Therapeutics
City of Hope

- *Consultant for Aveo, Inc., Eisai Inc., Exelixis Inc., and Pfizer, Inc.; Grant/Research Support from Tempus AI, Dendreon Pharmaceuticals LLC, and Fennec Pharmaceuticals Inc.*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of AMG509 (xaluritamig), PSCA CAR T, STEAP2 CAR T, pasritamig, luxdegalutamide, abbv-969, CEA immunocytokine, Ac225-CEA, Ac225-PSMA, INV-9956 (as part of phase I trial at Hoag), and JANX007 (as part of phase I trial at Hoag)

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *The translation of consent documents and availability of additional study forms in languages other than English.*
- *Strategies to reduce burden to patients living distant from cancer center (ex: rural populations) associated with participation in clinical trials.*
- *The inclusion of different cultural background in research protocols.*
- *The inclusion of non-English speaking patients in research protocols.*
- *Access to care.*

Prostate Cancer – Localized Disease

Case Presentation

A 75-year-old man with a prior history of BPH was diagnosed with localized prostate adenocarcinoma following elevated PSA in routine bloodwork. Biopsy showed Gleason 4+3=7 (Grade Group 3) in 6 of 12 cores, with a single 4-cm intraprostatic lesion (cT2aN0M0), iPSA12. There was no evidence of extracapsular extension or perineural invasion in his MRI and no distant disease on his CT scans.

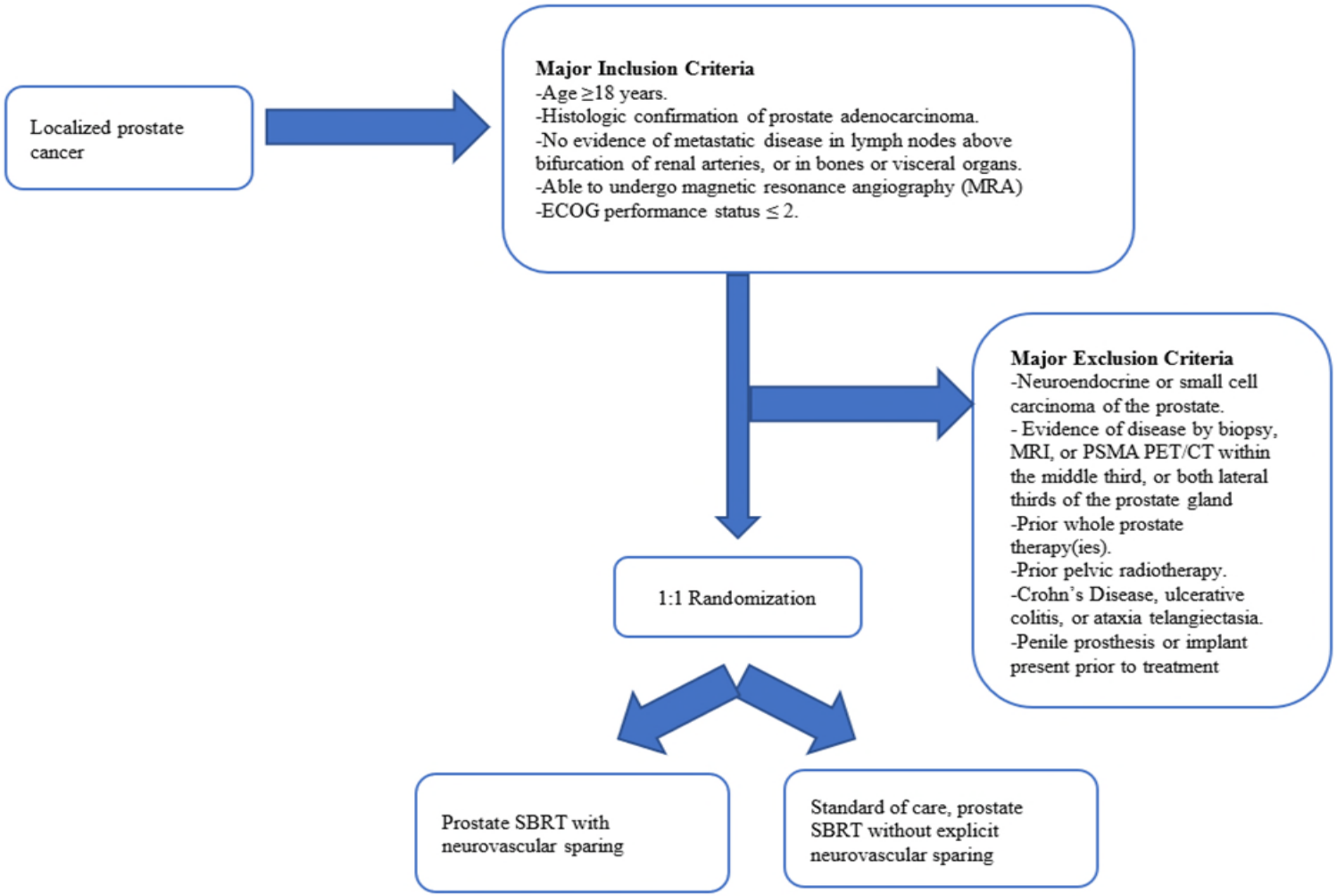
➡️**Localized prostate cancer, unfavorable intermediate risk.**

a) Standard of care SBRT (or IMRT) + 6 months of ADT

b) Clinical trial involving definitive radiation

c) Robotic-Assisted Laparoscopic Prostatectomy

d) Active Surveillance



Stratification
-Hormone Tx (none vs 4-6 m vs >6 m)
-Baseline use of ED meds (non vs baseline use)
-SBRT platform (CT-guided vs MRI-guided)
--Adaptive radiotherapy therapy (adaptive vs non-adaptive)

Vortex (IIT, ViewRay Sytems funded)
NCT07293585

Cliffsnotes:
For patients with localized prostate cancer receiving SBRT, we will deliver advanced neurovascular-SBRT (versus standard of care SBRT)

Discussion:
- Focal therapy trials in the region?
- Approach if PSMA PET+ in pelvic LN ?
- Genomically targeted trials?

Prostate Cancer – Metastatic Hormone Sensitive Disease

Case Presentation

A 70-year-old man was diagnosed with localized prostate adenocarcinoma following an acute urinary retention. Biopsy revealed Gleason 4+3=7 (Grade Group 3) disease in 8 of 12 cores, with an intraprostatic lesion measuring 5 cm and an initial PSA of 15. He underwent a robotic-assisted laparoscopic prostatectomy but later developed biochemical recurrence, with a PSA doubling time of 6 months. His Bone Scan was negative, however a follow-up PSMA PET demonstrated two avid lesions in the pelvis and one in his left scapula.

➡️ **Metastatic hormone-sensitive prostate cancer**

a) SBRT + ADT

b) ADT + ARPI

c) Clinical trial

d) Docetaxel + ADT + ARPI

Enzalutamide +/- PDS01ADC w/out ADT in PSMA PET+ recurrent prostate cancer

(NCT06096870)

LOMA LINDA UNIVERSITY HEALTH

Eligibility Criteria:

- S/p RALP or definitive RT
- PSMA+ PCa
- PSADT < 12 mo
- Testosterone >100 ng/dL
- No soft tissue dz and neg bone scan

R
1:1

Enzalutamide 160 mg daily
+
PDS01ADC 12 mcg/kg SQ Q28d

Enzalutamide 160 mg daily

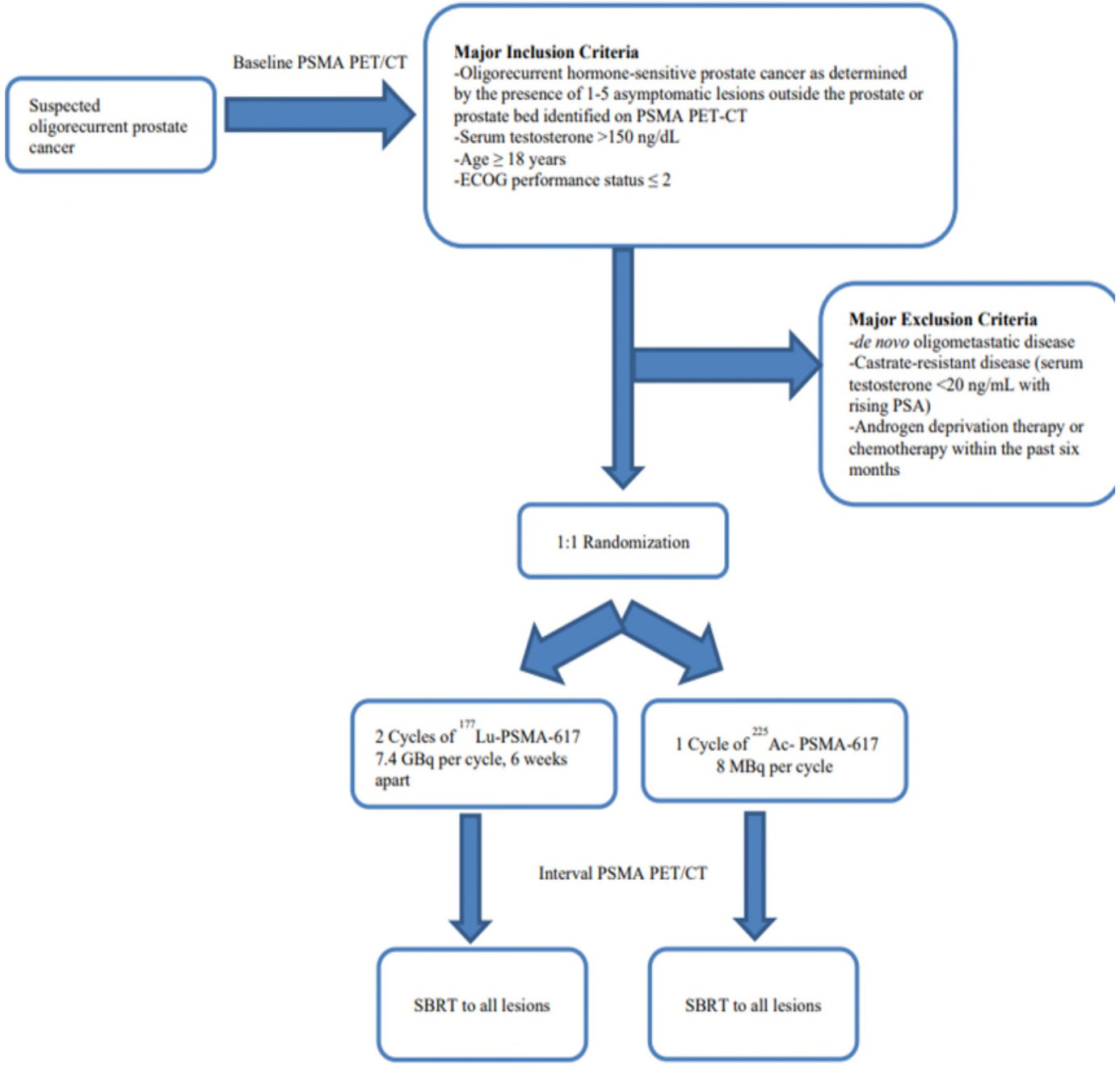
Primary Outcome:

- 5-year PSA control

Secondary Outcomes:

- PET changes
- Safety
- Eval of immune response
- Proportion PSA undetectable at 12 mo

- PDS01ADC is an IL-12-fused ADC that enhances NK cells and binds regions of tumor necrosis → drives local immune activation w/o requiring tumor-specific antigen
- 3 mo enzalutamide w/o ADT can control PSA for ~1yr in recurrent PCa
- Enzalutamide w/out ADT induces tumor necrosis and enhances NK cells, also makes PCa more sensitive to T-cell mediated lysis
- Rationale: “heat up” immunogenically cold tumor + AR inhibition to improve T cell responses & tumor control



ANDROMEDA (IIT, Novartis funded)
NCT07150715

"successor" trial to LUNAR

Cliffsnotes:
For patients with oligorecurrent mHSPC, 1:1 randomization to
2 cycles Pluvicto+SBRT
Vs.
1 cycle Ac225-PSMA-617 + SBRT

Discussion:
- SBRT +/- ADT
- EMBARK regimen

Case Presentation

A 72-year-old man presents with progressive back pain and weight loss. He has a PSA of 158 ng/mL and his CT scan revealed multiple bone lesions involving the spine, ribs, and pelvis, as well as a 6cm liver lesion. A liver biopsy confirms prostatic adenocarcinoma. Genetic testing showed MSS, TMB low, and no HRR alterations.

➡️ **High-volume metastatic hormone-sensitive prostate cancer**

a) Docetaxel + ARPI + ADT

b) Clinical trial

c) ADT + ARPI

d) ^{177}Lu-PSMA-617 + ADT + ARPI

A Phase II, randomized, open-label, multi-center study of JSB462 (luxdegalutamide) in combination with abiraterone in adult male patients with metastatic hormone-sensitive prostate cancer (mHSPC) - NCT06991556

Key Eligibility criteria

- ECOG 0-2
- High-volume mHSPC[1] by standard imaging
- No prior ARPI in the metastatic setting
- <90 days of ADT
- no neuroendocrine component
- eGFR>60

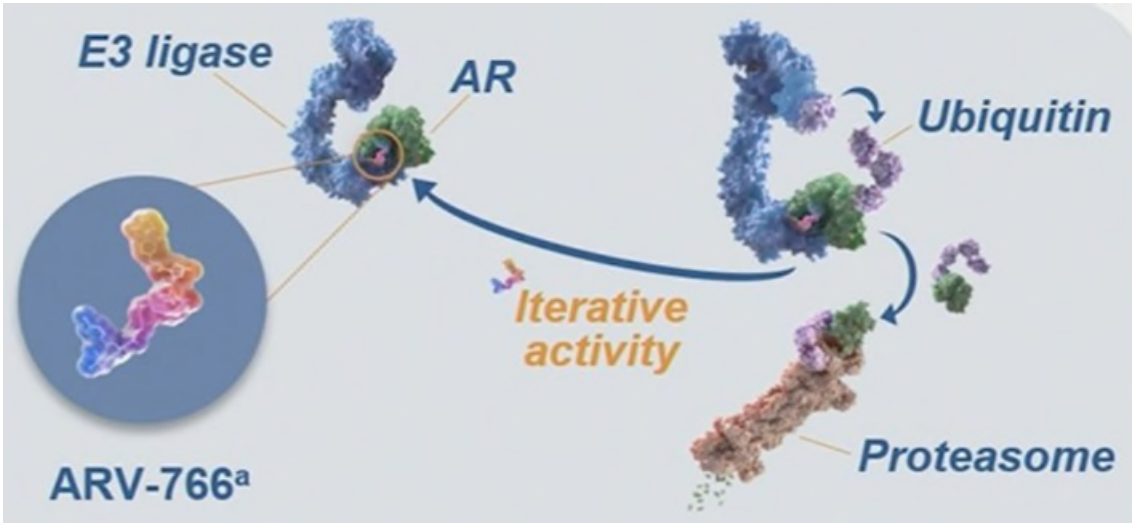
Arm 1: JSB462(100mg QD)+abiraterone (1000mg QD)
N=50

Arm 2: JSB462(300mg QD)+abiraterone (1000mg QD)
N=50

Arm 3: abiraterone (1000mg QD) or enzalutamide 160 mg/day
N=50

Primary endpoint:

PSA90 RR



Luxdegalutamide MOA

Legend:
1 - Visceral metastases and/or ≥4 bone lesions (with at least one outside the vertebral column and/or pelvis).
2 - Abiraterone 1000 mg QD /prednisone 5 mg/day or enzalutamide 160 mg QD per investigator's choice.
3 – Enzalutamide/abiraterone will be capped to 25 participants for each drug in arm 3.

Prostate Cancer – Metastatic Castration-Resistant Disease

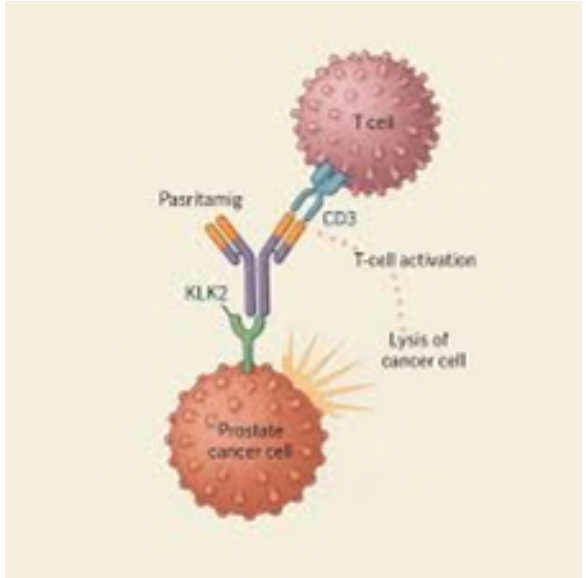
A Phase III, randomized, open-label study of Pasritamig (JNJ-78278343), a T-cell- redirecting agent targeting human kallikrein 2, with docetaxel versus docetaxel for metastatic castration-resistant prostate cancer - NCT07225946

Key Eligibility criteria

- ECOG 0-1
- mCRPC by standard imaging
- 1-2 prior ARPI
- no neuroendocrine component
- eGFR>30
- no prior chemo for PC in any setting
- no prior radioligands
- no prior Sip-T

Primary endpoint:

rPFS by BICR



Participants with mCRPC progressed on at least 1 ARPI

→ RANDOMIZATION

1:1
Open label
N=800

→ **PASRITAMIG every 6 weeks + DOCETAXEL 75 mg/m² every 3 weeks up to 10 doses**

→ **DOCETAXEL 75 mg/m² every 3 weeks up to 10 doses**

STRATIFICATION FACTORS

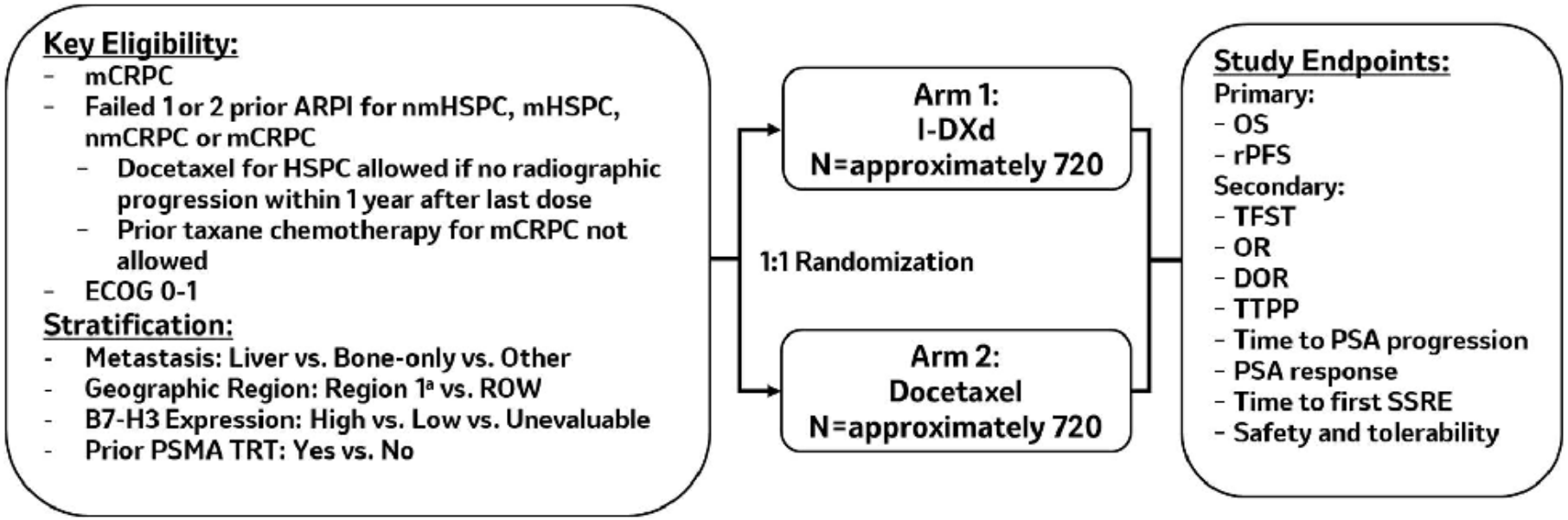
1) Site of metastases (non-visceral, visceral-liver or visceral-others)
2) LDH (normal vs abnormal)
3) ECOG (0 or 1)
4) Prior PARP inhibitor (yes or no)

Advanced/Metastatic

Open to Accrual

- UCI 24-158: A Phase III, Open-Label Study of Ifinatamab Deruxtecan Versus Docetaxel in Participants with **Metastatic Castration-Resistant Prostate Cancer (mCRPC)** (IDeate-Prostate01) - NCT06925737

Figure 1 Study Schema

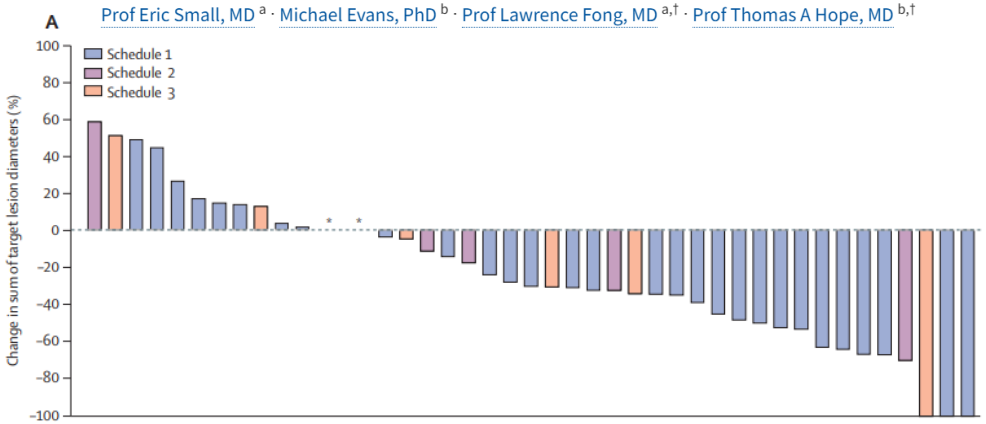


ARPI=androgen receptor pathway inhibitor; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EU=European Union; HSPC=hormone-sensitive prostate cancer; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; N=number of participants; nmCRPC=non-metastatic castration-resistant prostate cancer; nmHSPC=non-metastatic hormone-sensitive prostate cancer; OR=objective response; OS=overall survival; PSA=prostate-specific antigen; PSMA=prostate-specific membrane antigen; ROW=rest of the world; rPFS=radiographic progression-free survival; SSRE=symptomatic skeletal-related event; TFST=time to first subsequent therapy; TRT=targeted radionuclide therapy; TTPP=time to pain progression; UK=United Kingdom, USA=United States of America.

[a] Region 1=USA, UK, EU, Switzerland, Israel, Australia, Japan, and South Korea. Additional countries may be added as the study progresses.

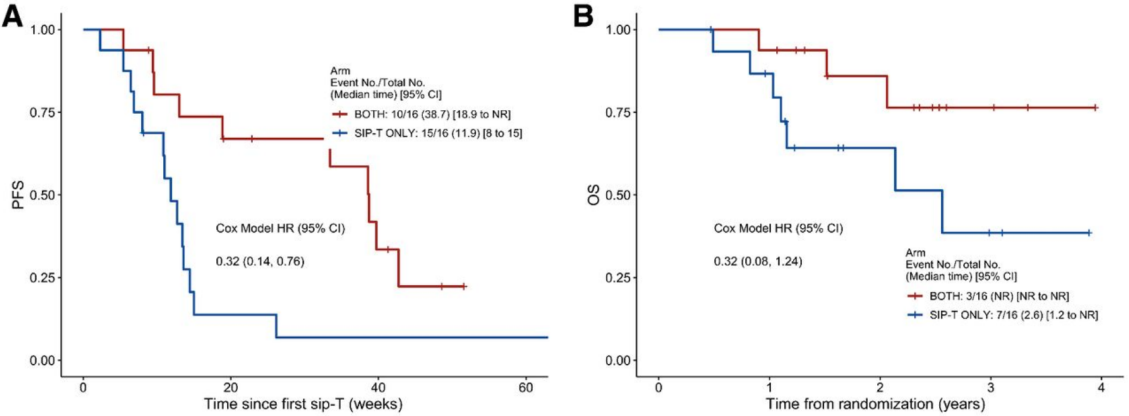
Single-dose ^{177}Lu-PSMA-617 followed by maintenance pembrolizumab in patients with metastatic castration-resistant prostate cancer: an open-label, dose-expansion, phase 1 trial

Prof Rahul Aggarwal, MD [a] · Stephanie Starzinski, BS [a] · Ivan de Kouchkovsky, MD [a] · Vadim Koshkin, MD [a] · Rohit Bose, MD [a] · Jonathan Chou, MD [a] · Arpita Desai, MD [a] · Daniel Kwon, MD [a] · Samuel Kaushal, BS [a] · Lauren Trihy, BS [a] · Medini Rastogi, BS [a] · Robin Ippisch, PhD [b] · Maya Aslam, BA [b] · Prof Terence Friedlander, MD [a] · Prof Felix Feng, MD [a] · David Oh, MD [a] · Alexander Cheung, BS [a] · Prof Eric Small, MD [a] · Michael Evans, PhD [b] · Prof Lawrence Fong, MD [a,†] · Prof Thomas A Hope, MD [b,†]



Randomized Phase II Trial of Sipuleucel-T with or without Radium-223 in Men with Bone-metastatic Castration-resistant Prostate Cancer

Catherine H. Marshall; Wei Fu; Hao Wang; Jong Chul Park; Theodore L. DeWeese; Phuoc T. Tran; Daniel Y. Song; Serina King; Michaella Afful; Julia Hurrelbrink; Charlotte Manogue; Patrick Cotogno; Nancy P. Moldawer; Pedro C. Barata; Charles G. Drake; Edwin M. Posadas; Andrew J. Armstrong; Oliver Sartor; Emmanuel S. Antonarakis



Pilot Study of ^{177}Lu-PSMA-617 in Combination with Sipuleucel-T in Patients with Metastatic Castration-Resistant Prostate Cancer

Key Eligibility Criteria:
- Diagnosis of metastatic castration resistant prostate cancer
- Progression on at least one androgen receptor pathway blocker

DAY 0

2:1 Randomization

Arm A (n=10):
Lutetium Lu 177 vupivotide tetraxetan
Q6W x 6

Arm B (n=20):
Lutetium Lu 177 vupivotide tetraxetan
Q6W x 6

WEEK 8

Arm B (n=20):
Sipuleucel-T
Q2W x 3

*rPFS, OS will be measured from date of randomization for the intent-to-treat population

Primary Objective(s)

- To evaluate the immune response induced by the combination of ^{177}Lu-PSMA-617 and Sipuleucel-T, using changes in anti-prostatic acid phosphatase (PAP) IgG antibody titers.

Secondary Objective(s)

- To evaluate anti-PA2024 antibody titers in patients receiving ^{177}Lu-PSMA-617 alone versus in combination with Sipuleucel-T.
- To assess the safety and tolerability of ^{177}Lu-PSMA-617 plus Sipuleucel-T.
- To characterize the pharmacokinetics (PK) of ^{177}Lu-PSMA-617 plus Sipuleucel-T in the blood.
- To evaluate the clinical efficacy of ^{177}Lu-PSMA-617 alone versus in combination with Sipuleucel-T.
- To determine the impact of ^{177}Lu-PSMA-617 in combination with Sipuleucel-T on systemic immunomodulation.

Case Presentation

A 68-year-old man presents with progressive back pain and weight loss. He has a PSA of 110 ng/mL and multiple bone metastases involving the spine, pelvis, and retroperitoneal lymph nodes showed in his CT scans. A bone biopsy confirms prostatic adenocarcinoma. He was initially treated with ADT + abiraterone until he experienced PSA and radiographic progression with PSMA avid disease to the right lung. Re-biopsy with genetic testing revealed AR mutation (L702H). He was switched to docetaxel, however had a new progression to the lungs and chest lymph nodes after 8 cycles. Re-biopsy showed no neuroendocrine differentiation, MSS, and no HRR alterations.

➡️ **Metastatic castration-resistant prostate cancer s/p ARPI and docetaxel**

a) Cabazitaxel

b) Clinical trial

c) Cabazitaxel + carboplatin

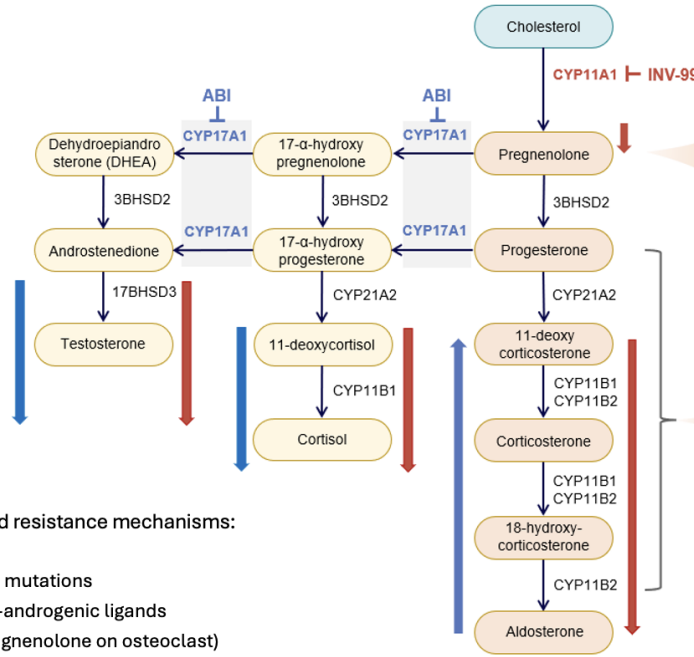
d) ^{177}Lu-PSMA-617

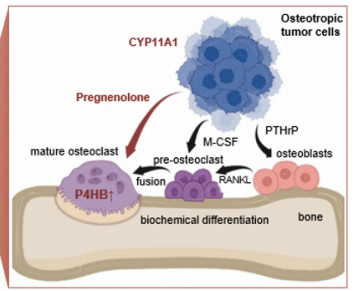
A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Antitumor Activity of INV-9956 in Adult Patients with Advanced Metastatic Castration Resistant Prostate Cancer - NCT06609005

CYP11A1 Inhibition Potentially Addresses CRPC Treatment Resistance

- **Inhibits steroid biosynthesis, prevents promiscuous activation of AR signaling**
- **Has the potential to suppress bone metastasis**

- CYP11A1 converts cholesterol to pregnenolone, the common precursor to all steroids, including androgens
- CYP11A1 inhibition blocks steroid biosynthesis, a novel therapeutic strategy to treat CRPC
- Intratumoral production of pregnenolone through CYP11A1 is reported to promote bone metastasis formation and tumor-induced osteolysis





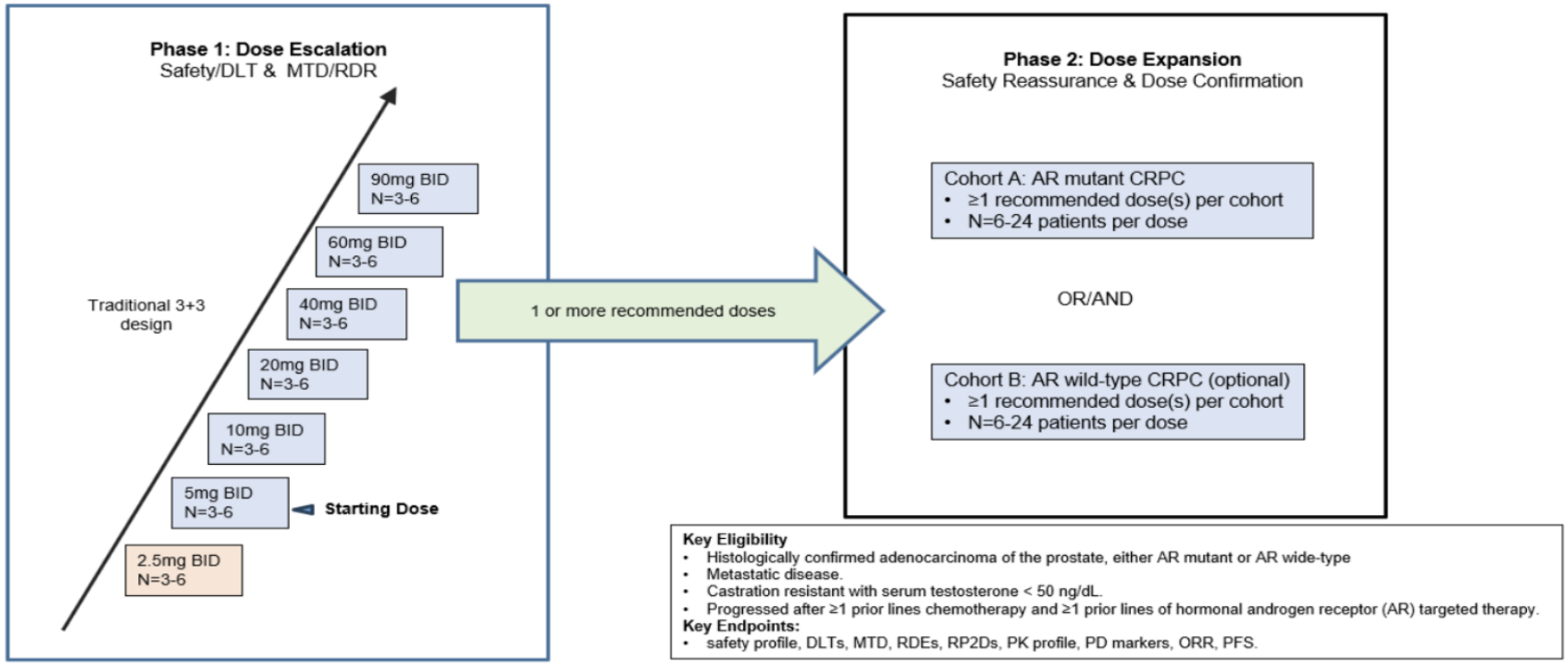
Adapted from Cell Reports, 2024, 43(3).

Steroid Promiscuity
Promiscuous activation of Androgen receptor signaling

- Effect on CRPC with clinically acquired AR-related resistance mechanisms:
  - AR amplified CRPC
  - CRPC with anti-androgen agonist-switching AR mutations
  - Activation of AR by corticosterone or other non-androgenic ligands
  - Possibility of reducing bone metastasis (via pregnenolone on osteoclast)

Reference:
British journal of cancer, 2009, 100(5): 671-675;
JCEM Case Reports, 2023, 1(2): luad039.

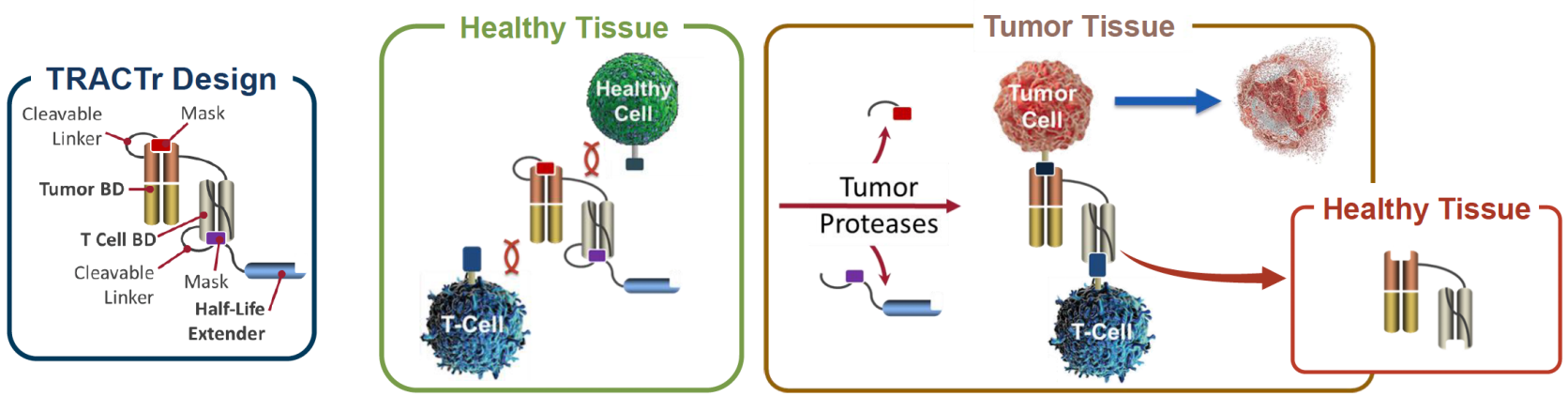
A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Antitumor Activity of INV-9956 in Adult Patients with Advanced Metastatic Castration Resistant Prostate Cancer - NCT06609005



Study of JANX007 in Subjects with Metastatic Castration-Resistant Prostate Cancer (ENGAGER-PSMA-01) - NCT05519449

Janux Tumor Activated T-Cell Engager (TRACTr) platform design principles

Each program is designed as a potent T-cell engager with reduced toxicity



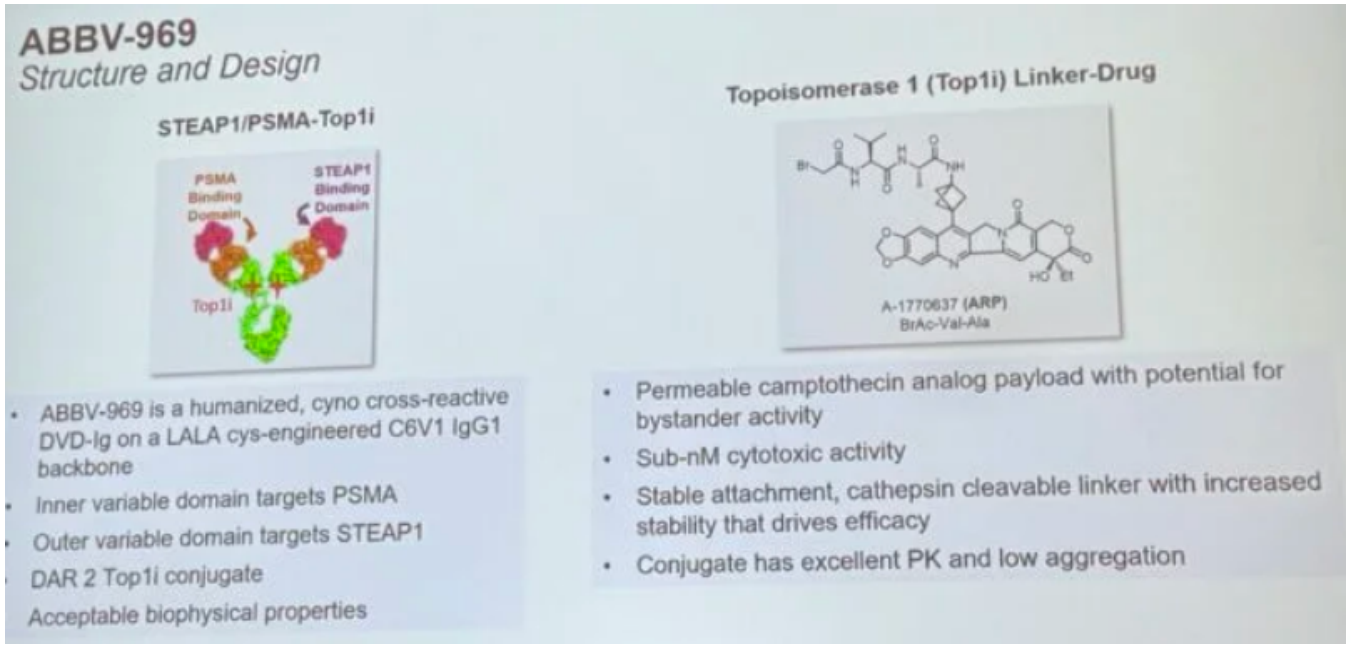
Masks block activity against healthy tissues to reduce CRS and on-target, healthy tissue toxicity

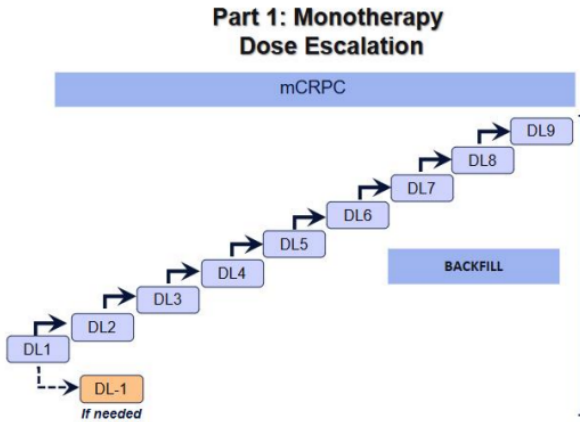
Tumor specific activation to maximize anti-tumor immune response

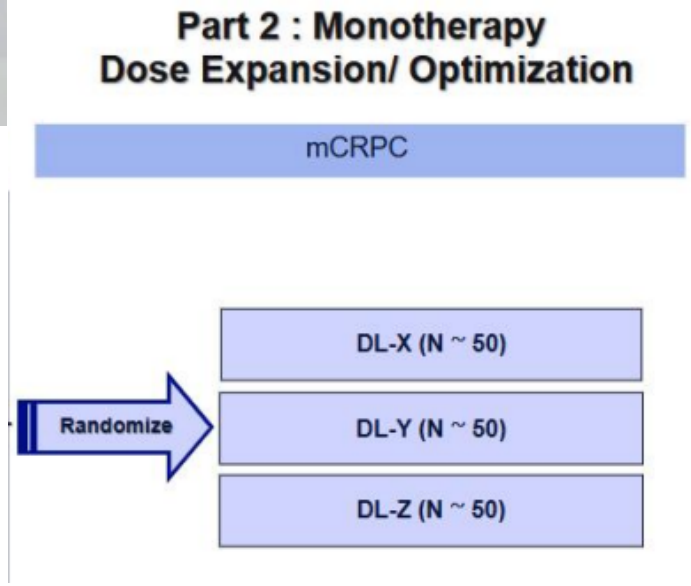
TCE is rapidly cleared from healthy tissue to limit systemic toxicity

Emerging JANX007 clinical data demonstrates TRACTr platform can potentially improve both safety *and* efficacy compared to contemporary TCEs

Metastatic Castration-Resistant Prostate Cancer: First-in-Human Study of ABBV-969 in Metastatic Castration-Resistant Prostate Cancer





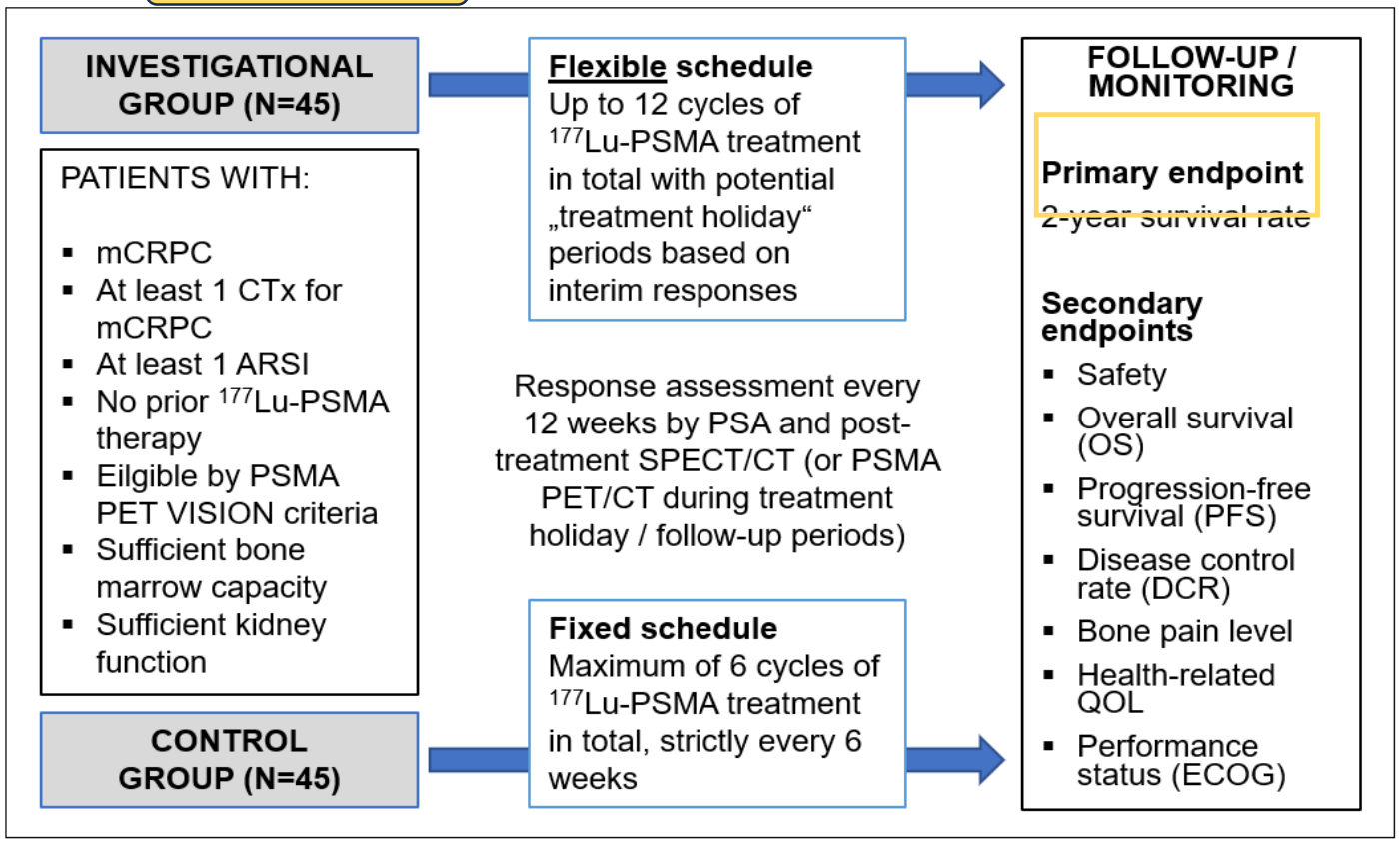


Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of ABBV-969 as monotherapy in mCRPC	• Safety will be evaluated based upon the assessment of all grade AEs, grade 3+ AEs, DLTs, and SAEs reported during the TEAE period; clinical laboratory parameters (e.g., hematology, chemistry); vital sign measurements; and ECG results.
Secondary	
• To evaluate the preliminary efficacy of ABBV-969 as monotherapy in subjects with mCRPC	Primary Efficacy Endpoint: • Achieving PSA response (≥ 50% PSA decrease from baseline)

3 mg/kg
5 mg/kg
8 mg/kg

FLEX-MRT: a prospective phase 2, parallel group, randomized, controlled, oen-label, single-center trial in men with mCRPC to **determine the efficacy of a flexible dosing schedule of ^{177}Lu-PSMA therapy up to 12 cycles in comparison to the standard regimen of 6 cycles.**

Study Design



FLEX-MRT (Novartis funded)
NCT 06216249

Cliffsnotes:
For patients with mCRPC, we will deliver standard duration 6 cycle Pluvicto vs. dosing up to 12 cycles with potential holiday based on response.

Discussion:

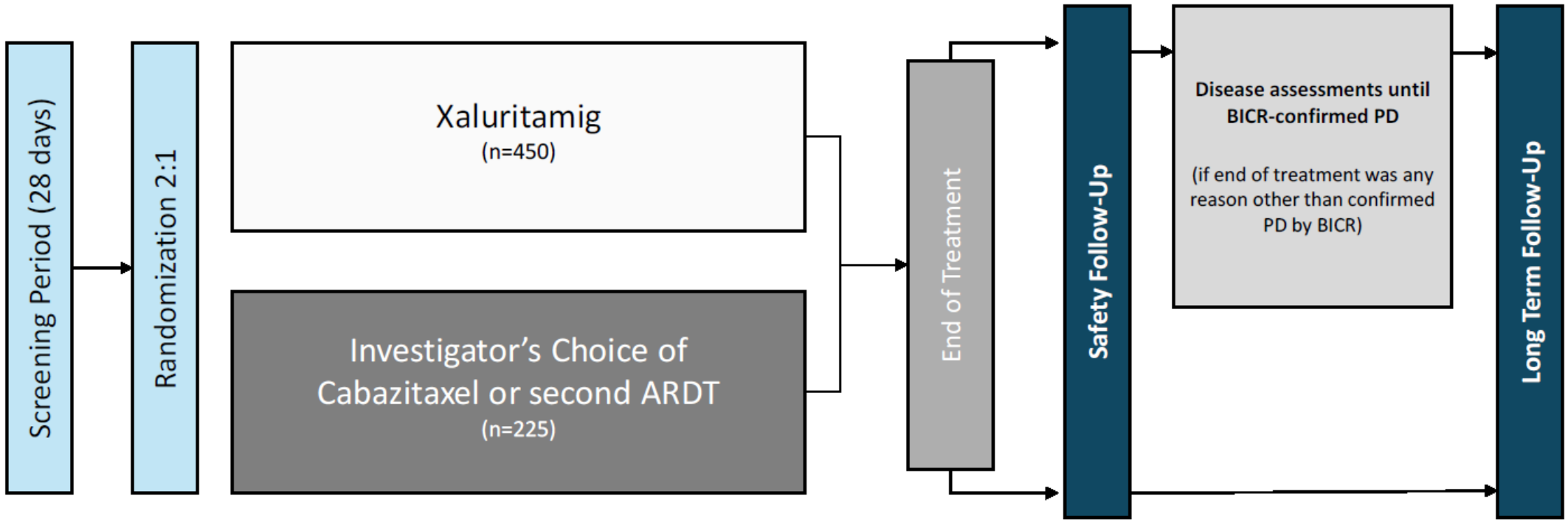
- How is Pluvicto currently being dosed?
- Interest in taxane chemo vs “smart chemo” ADC

Advanced/Metastatic

Open to Accrual – NCT06691984

- UCI 24-79: A Phase III, Open-Label, Multicenter, Randomized Study of Xaluritamig vs Cabazitaxel or Second Androgen Receptor-Directed Therapy in Subjects With **Metastatic Castration-Resistant Prostate Cancer** Previously Treated With Chemotherapy

Figure 1-1. Study Schema



ARDT = androgen receptor-directed therapy; BICR = blinded independent central review; PD = progressive disease.

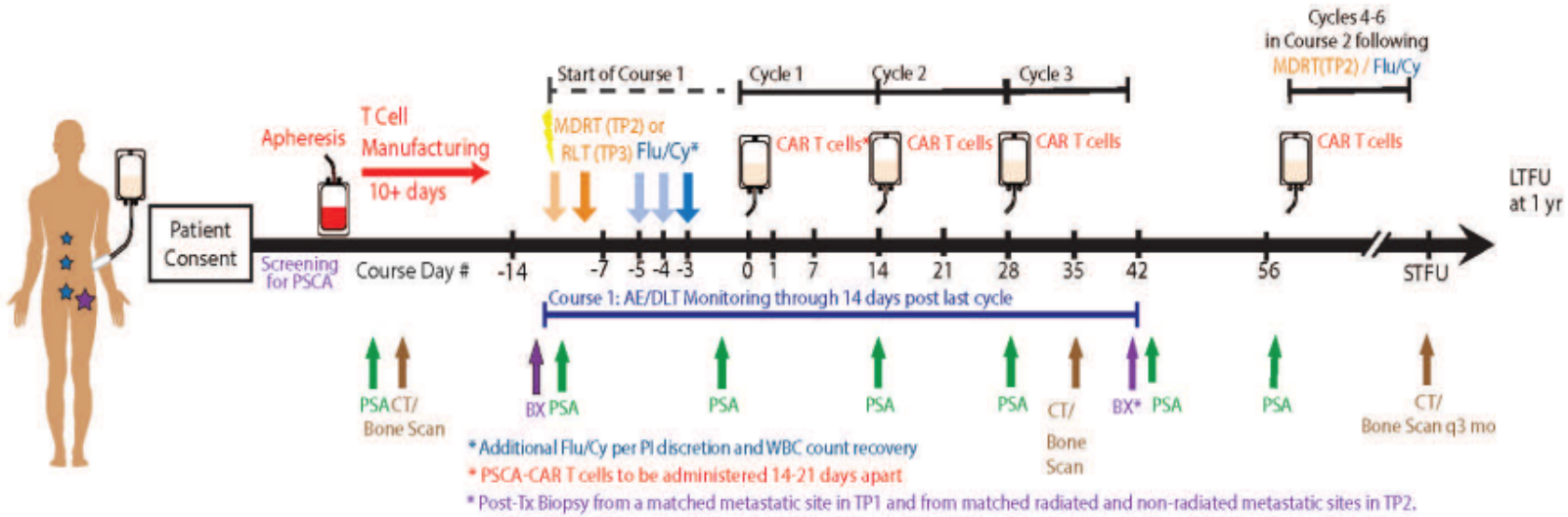
Phase 1b Study Evaluating Combinations with PSCA-targeting Chimeric Antigen Receptor (CAR)-T cells for Patients with Metastatic Castration-Resistant Prostate Cancer - NCT05805371

Primary Objectives:

- Assess the feasibility, safety, and activity of lymphodepleting chemotherapy followed by up to 3 cycles of 50M PSCA-CAR T cell immunotherapy per course either alone (TP1) or in combination with metastasis directed RT (MDRT = TP2)

Key Eligibility:

- Documented castration resistant prostate cancer (mCRPC)
- At least one prior advanced androgen targeted therapy
- Documented PSCA+ tumor expression
- In case of prior chemotherapy, at least 2 weeks must have elapsed prior to leukapheresis
- ECOG performance status 0-2



Prostate Cancer – NEPC

Case Presentation

A 52-year-old man presents with weight loss and is found to have PSA 39, sclerotic bone lesions, and a 3-cm right lung nodule. Lung biopsy confirms metastatic prostate adenocarcinoma. He starts abiraterone + ADT, with PSA falling to 2.0. After six months, PSA rises to 3.2. Imaging shows PSMA-negative disease with growth of the lung lesion and stable bone lesions. Repeat lung biopsy reveals small cell prostate cancer. Genomic testing is MSS, TMB-low, and HRR-negative. He receives four cycles of cisplatin + etoposide and SBRT to the lung lesion. Six months later, he is found to have a new contralateral 4-cm lung nodule as well as a new 5-cm liver lesion, PSA 5.2 and CEA 105 ng/ml.

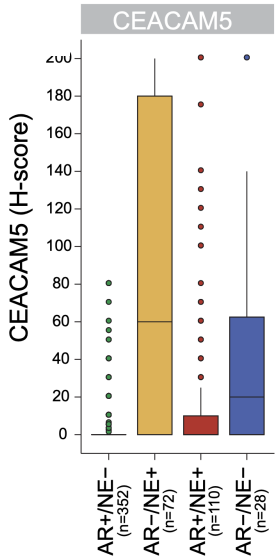
➡️ **Metastatic castration-resistant prostate cancer with small cell differentiation**

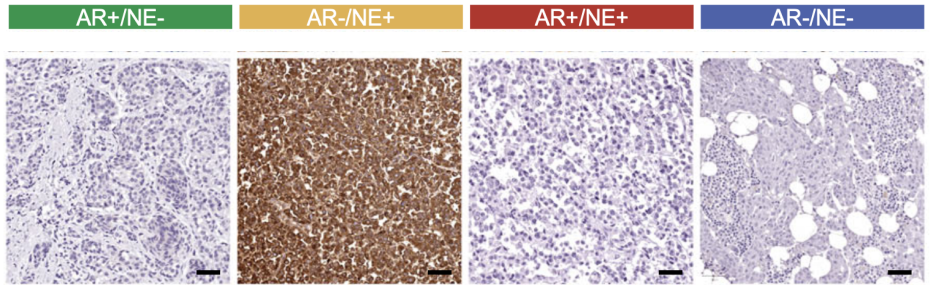
a) Docetaxel

b) Re-challenge with platin containing regimen

c) Clinical trial evaluating CEACAM5-targeted immunocytokine

d) Nivolumab

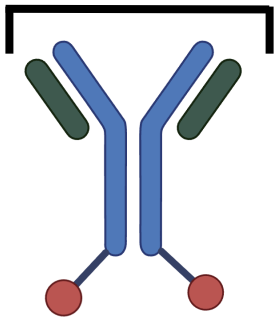




CEACAM5 is **commonly expressed** in **androgen-indifferent prostate cancers** such as neuroendocrine (NEPC) and double-negative (DNPC) subtypes

Ajkunic et al. NPJ Precis Oncol 2024

CEACAM5 binding domain

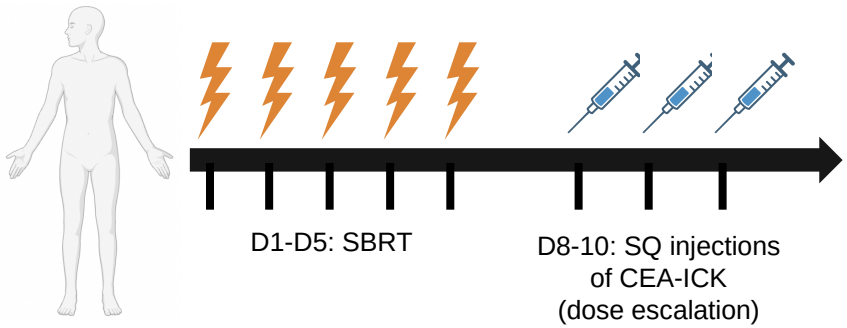


Conjugated IL-2 cytokine

Novel CEACAM5-targeted immunocytokine (CEA-ICK) developed at City of Hope

Phase 1 study of SBRT plus CEA-ICK (NCT06130826)

- Refractory NEPC (AR-/NE+) and DNPC (AR-/NE-)
- No restrictions on prior chemo or radioligand therapy
- CEA-positive disease: serum CEA ≥ 5 ng/mL or positive CEA staining on IHC
- At least 5 metastatic sites amenable to SBRT



- Primary endpoint: determine the RP2D of immunocytokine
- Secondary endpoints: objective response rate, rPFS, immune correlates, and integration of immuno-PET imaging

PROSTATE CANCER FOUNDATION PCF CURING TOGETHER

Mentors: Tanya Dorff, John Shively, and Jeffrey Wong